Health Disparities and Prostate Cancer: Can Educational Status, Race and Geographical Distance to Care Facilities Impact Risk and Severity on Initial Biopsy?

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Elizabeth L. Turner

Thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science in the Duke Global
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ABSTRACT

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Abstract

Introduction: Prostate Cancer (PC) screening has become a controversial topic both in the United States and abroad, stimulating debates surrounding who should and should not be screened. United States (USA) population-based studies have established a link between race and PC risk, but whether race predicts PC after adjusting for clinical characteristics is unclear. In Brazil, where cancer registries are limited, underprivileged men have limited access to both education and health care due to geographic barriers. Thus, we investigated the association between, educational status, geographic distance from screening site to follow-up care facility and non-compliance with having cancer, and, risk of low and high-grade PC in men undergoing initial prostate biopsy in equal access medical centers in the USA and Brazil.

Materials & Methods: In our first analysis, we conducted a retrospective record review of 887 men (49.1% black, 50.9% white) from the Durham Veterans Affairs Medical Center (DVAMC) who underwent initial prostate biopsy between 2001 and 2009. Multivariable logistic regression analysis of race and biopsy outcome was conducted adjusting for age, body mass index (BMI), number of cores taken, prostate specific antigen (PSA), and digital rectal exam (DRE) findings. Multinomial logistic regression was used to test the association between black race and PC grade (Gleason <7 vs. ≥ 7). Our second analysis used data from the Barretos Cancer Hospital (BCH) screening study, another retrospective record review of 1,561 men who were recommended to prostate

biopsy after obtaining an initial screen on the medical mobile units between 2004 and 2007. Multivariable logistic regression analysis of geographic distance from screening site to BCH (km), maximum level of education achieved, and risk of non-compliance was performed adjusting for age and calendar year of biopsy. Among those who complied with biopsy recommendations and received a biopsy (n=850), multivariable logistic regression analyses were conducted to test the association between geographic distance, educational achievement and having PC. Of those men with PC, a multinomial logistic regression test was used to evaluate the association between geographic distance, educational attainment and risk of low and high-grade PC (Gleason <7 vs. ≥7).

Results: In the DVAMC study, Black men were younger at biopsy (median: 61 vs. 65 years, p<0.001), and had a higher pre-biopsy total PSA (tPSA, median: 6.6 vs. 5.8ng/ml, p=0.001) than white men. A total of 499 (56.3%) men had PC on biopsy (245 low-grade; 254 high-grade). In multivariable analyses, black race was significantly predictive of PC overall (odds ratio, [OR]: 1.50, 1.12 – 2.00, p=0.006), and high-grade PC (relative risk ratio [RRR]: 1.84, 1.28 – 2.66, p=0.001), but was not significantly associated with low-grade PC (RRR: 1.29, 0.92 – 1.80, p=0.139). In the BCH studies, non-compliant men were older at initial screen (median: 68 vs. 66 years, p<0.001), had a higher tPSA (median: 4.90 vs. 4.2 ng/mL, 0<0.001), were less likely to have an abnormal DRE (19.5% vs. 33.4%, p<0.001), had less education (low education: illiterate or incomplete primary, vs. high education: complete primary, high school or college, 1,402 vs. 159,

p=0.14, data not shown) and were more likely to live more than 500km from BCH (66.3% vs. 19.6%, p<0.001) when compared to men who complied with biopsy recommendations. On crude and multivariable analyses, non-compliance was significantly associated with increased distance from screening site to BCH relative to traveling less than 250km for care (250-500km: OR: 2.00, 500-1000km: OR: 5.88, >1000 km: OR: 15.98, p<0.001). On crude and multivariable analysis, increased educational attainment relative to being illiterate had a protective association with non-compliance (incomplete primary: OR: 0.53, complete primary: OR: 0.33, p<0.001, high school + college: OR: 0.87, p=0.64). Of the screened men who were recommended to and had an initial biopsy, 320 men had cancer (207 low-grade, 113 high-grade). Stratified by educational status, illiterate men were older at biopsy (median: 69 vs. 65 vs. 64 vs. 58 years, p<0.001), and had a higher tPSA at screening (median: 6.04 vs. 4.47 vs. 4.73 vs. 4.16, p=0.001). There were no differences, based on education, distance from screen site to Barretos (p=0.43), year of screening (p=0.08), number of abnormal DREs (p=0.42) or family history of cancer, especially PC (p=0.07). Before biopsy, confirmatory median tPSA was 7 (IQR: 4 – 16 ng/mL). With respect to PC on initial biopsy, there was no association between distance from screening site to BCH (relative to < 250km) and increased education achievement. On multinomial analysis, educational achievement showed an association with neither low nor high-grade cancer relative to no cancer. There was no association between increased distance and low-grade PC. There was no association between traveling 500-1000km (p=0.96) or ≥1000km (p=0.15) and high-

grade cancer; however, there was a significant association between traveling 250-500km relative to ≤250km and high-grade PC risk (RRR: 2.44, 95% p=0.04).

Conclusion: In a USA-based equal access health care facility, black race was associated with greater risk of PC detection on initial biopsy and of high-grade cancer after adjusting for clinical characteristics. In Brazil, where cancer data are limited, education and geographic distance from point of screening to care facility are not associated with having PC on biopsy or biopsy grade. Distance was, however, significantly associated with risk of non-compliance after primary screen. Thus, additional investigation of mechanisms linking black race and PC risk and PC aggressiveness is needed.

Dedication

I would like to dedicate this work to the men of the United States military and the thousands of Brazilian men and volunteers who gave their time and agreed to share their health information for these projects to be possible. Without you, we could not advance our understanding of the epidemiology of prostate cancer. For that, I thank you.

Acknowledgements

This work would not have come to fruition without the guidance and assistance of so many people. To each of you, I am sincerely grateful for the time you have devoted to teaching, guiding, and supporting me, but most importantly, for helping me to achieve my dreams.

First and foremost, I would like to thank my family and friends for their unconditional love and support through my thesis process and the first part of my graduate school career. To my parents, Edith Young and Mosely Gaines, Jr., I would not be here without you, and I will never be able to repay you for everything you have done for me. As I continue through my career, I would like you to know that I am honored to be your daughter and I am inspired by your work ethic, accomplishments and dreams. I love you both, more than words can say.

I was incredibly fortunate and honored to have my thesis committee led by Dr. Cathrine Hoyo, who not only inspired me to chase my dreams, but also pushed me to generate the best work I could for this thesis and my future graduate career. Without your guidance, friendship, and immeasurable patience, I would not have realized my true career path and developed a network of collaborations that helped me generate this thesis. Thank you for all you have done for me and generating insightful works which pave the way for future generations to build upon. You are irreplaceable and I thank you.

To my amazing thesis committee, Dr. Patricia (Trish) Moorman and Dr. Elizabeth (Liz) Turner, I could not have asked for a more inspiring group of women to work with. You each brought knowledge and uniqueness to my committee, which allowed me to follow my instincts, curiosity, and further my projects. As a graduate student, having that kind of support is invaluable.

I would also like to thank Dr. Stephen J. Freedland for providing me access to the datasets on which my thesis is based, but also being a mentor, a sounding board, and a friend. You were one of the first to believe in me and help me navigate through the process of becoming an independent researcher. Your infectious passion for understanding science and its applications while continuing to grow as a leader is an inspiration. I will never be able to thank you enough for the unconditional support you have provided me during my career at Duke and for continuing to support my motivation to excel.

Additionally, I have been fortunate enough to have several wonderful collaborators who have dedicated their time and efforts to review these works, provide insight, guidance, and be a sounding board for a developing researcher like me. Without you and your expertise, we would not be able to push the envelope and make a contribution to science. Thus, I thank, in no particular order: Dr. Roberto Müller, Dr. Adriana C. Vidal, Dr.

Eliney F. Faria, Dr. Delores J. Grant, Dr. Susan K. Murphy, Dr. David Skaar, and Dr. Christopher J. Keto.

Finally, but certainly not least, to the Duke Global Health Institute and its esteemed leaders, Dr. Christopher W. Woods, Dr. Brian Pence, and Sarah Martin: I am so honored to graduate from this program and to have been able to learn from each of you. The time I spent with each of you helped to shape my graduate career and help me cultivate my passions. You are amazing educators and I thank you for all you do.

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List of Abbreviations

ANOVA: analysis of variance statistical test

AUA: American Urological Association

BCH: Barretos Cancer Hospital, Barretos, São Paolo, Brazil

BMI: body mass index measured in kg/m^2

Bx: biopsy

CI: confidence interval

CC: cubic centimeter (cm^3)

DRE: digital rectal exam

DVAMC: Durham Veterans Affairs Medical Center, Durham, North Carolina, USA

fPSA: free PSA measured in ng/mL

IQR: interquartile range

Kg: kilogram

Km: kilometer

M: meter

mL: milliliter

Ng: nanogram

OR: odds ratio

RRR: relative risk ratio

P: p-value

PC: prostate cancer

pfPSA: percent-free PSA measured as fPSA/tPSA * 100%

PSA: prostate specific antigen measured in ng/mL

tPSA: total prostate specific antigen measured in ng/mL

TRUS: transrectal ultrasound

1. Introduction

1.1. Prostate Cancer

A slow growing cancer with no symptoms until in its most advanced stages, prostate cancer (PC) is the most commonly diagnosed among men in the developed world with a steadily increasing burden worldwide.[1, 2] While incidence rates increased drastically in the early 1990s[3], the result of widespread acceptance and use of prostate specific antigen (PSA) testing as a mean of cancer detection, the burden of disease is disproportionately distributed among developed countries relative to developing.

1.2. Disease Burden

The role of cancer in the global sphere is steadily increasing despite rapid declines in cancer death rates in developed countries.[1] This phenomenon could be the result of increased life expectancies[4], adoption of economic-based cancer-causing behaviors such as poor diet and nutrition[5], smoking[6, 7], and lifestyle factors such as alcohol consumption and physical inactivity[8]. The apparent increased incidence could also be due to overdiagnosis, the result of increased availability and use of screening technologies to detect early stage disease.[9, 10] While an estimated 30% of cancers are preventable in spite of these factors, what is clear is that understanding patterns of disease burden can ultimately lead to better strategies for prevention and intervention.[11]

PC incidence rates vary worldwide by almost a factor of 25[12], due in part to the disproportionate use of the PSA test in areas such as Australia, the US, and Europe, though there were substantial differences in PC incidence pre-PSA testing.[13] After the widespread use of the PSA test in these areas in the 1990s, temporal trends in incidence rates rose drastically as more cancers, both indolent and otherwise, were being detected with the use of this technology, then quickly declined as the result of advances in treatment and management.[14] Despite these incidence trends, mortality rates are highest among men on African descent in the US and Caribbean, implicating a genetic phenomenon in the role of PC-mediated deaths.[15-17] Interestingly, while men of African descent have higher PC mortality rates, the fact that the highest incidence rates occur in westernized countries suggests a multifactorial etiology of PC inclusive of both lifestyle/diet and genetics. While it is uncertain what specifically contributes to increased risk, likely some combination of the aforementioned plays a role in the development and progression of PC.

1.3. Screening

1.3.1. Prostate Specific Antigen Screening

Developed in the 1980s to monitor disease progression of men with PC, the PSA test measures the amount of protein generated by the prostate in whole blood. Typically

elevated in men with PC, benign prostatic hyperplasia, and prostatitis, the PSA test is most commonly used in conjunction with DRE screening to detect PC. Measured in units of ng/mL, the PSA test lacks the ability to differentiate among PSA increases generated from aggressive cancers, indolent cancers that will never progress, and the aforementioned benign conditions.

PSA exists in the blood in very low concentrations and requires highly sensitive measures to calculate it. Men have a combination of both "free" protein in the blood (fPSA) and bound protein. tPSA is defined as the sum of fPSA plus the proportion of it that is bound to other complexes. tPSA is typically measured by the PSA test. For men whose tPSA is between 2.5 – 4.0ng/mL (i.e. slightly elevated tPSA and suspicious of PC), pfPSA is included as a secondary measure of PC risk. Literature has shown that men with lower pfPSA, for example <15%, are at higher risk of PC.[18-20] The PSA ratio (pfPSA) is calculated by the amount of fPSA divided by tPSA.

1.3.2. Digital Rectal Exam Screening

A digital rectal exam (DRE) is an exam performed by a physician during which two digits are inserted into a man's rectum to examine his prostate. The prostate, a typically smooth gland, is then felt for nodules, which indicate abnormal growths on the surface, typically of cancer. The most basic way of diagnosing prostate abnormalities, DREs are

used worldwide to detect PC despite the fact that most tumors are not localized enough to determine PC by touch. This observation indicates that most early stage PCs are missed by DRE alone, and that diagnosis requires the use of alternative testing to confirm disease presence. Challenges with the DRE exam include low sensitivity, provider differences in what constitutes a tumor or not, and the patient's psychological stress related to the exam.[21]

1.3.3. Prostate Biopsies

A prostate biopsy is a procedure that removes small tissue segments from a prostate gland that is suspicious of cancer. Biopsies are conducted once a subject has undergone PSA and DRE screening and are the only way to diagnose or rule out PC after a positive PSA test. However, there are risks, such as infection, associated with biopsies. Lower cutpoints for PSA positivity have the trade-off of higher sensitivity for PC but more false positives, leading to more biopsies.

The procedure is typically performed transrectally using ultrasound as a guide to identify locations to be sampled. Transrectal ultrasounds also provide measurements for prostate volume. While the number of biopsy cores taken is not fixed, contemporary biopsy schemes recommend taking 12 "cores" – i.e. segments of tissue removed from the prostate via needles – per patient relative to older schema, which only took six. Some

investigators have suggested that increased numbers of positive prostate biopsies seen in contemporary cohorts could be the result of the changes to the biopsy scheme, from 6-8 cores in the 1990s to the current 12-core system, validating the effectiveness of this system-wide change.[22]

Biopsy outcomes are determined pathologically by the Gleason Score grading system.[23] Gleason scores range from 2 to 10, with higher scores indicating a worse prognosis. The score is given as the sum of two integers describing the grade (differentiation) of the tumor specimen. The first number describes the most common pattern of differentiation in the tumor and the second number describes either the next most common pattern or the highest grade seen in the specimen. These scores are then integrated into clinical practice to determine the best course of treatment action whether it is active surveillance, surgery, radiation, hormone or chemotherapy.

1.4. Risk Factors

Though PC etiology remains unclear, widely accepted risk factors such as increased age, PC family history, and PSA levels typically greater than or equal to 4ng/mL, have been shown to have be independent predictors of cancer.[24,25] Competing risk factors such as high body mass index (BMI), poor diet, poor nutrition[26] and lack of mechanistic studies make it hard to determine exact causes of disease and most men diagnosed eventually die

of something else. Currently of debate among practitioners, is the ability to predict clinical outcomes of patients for prevention and diagnostic purposes. Several established nomograms such as the American Urological Association (AUA) symptom score chart[27] and the Partin Tables[28, 29], utilize confirmed PC risk factors to help clinicians evaluate whether a patient is at risk or at high-risk for PC at presentation.

1.4.1. Health Disparities

Health disparities are gaps in quality of care, outcomes, or health status that are often the result of measurable inequalities in health care services received or rendered. Sociodemographics, economic status, and education are all factors, which can influence the abundance of health disparities and no doubt severity of cancer at initial presentation.[30, 31] Demographically speaking, black men have a lower socioeconomic status, less education, and lower-paying jobs than their white counterparts, thus limiting their access to health-care and screening facilities and affects PC outcome.[32]

While generalized health disparities are not just limited to socioeconomic status, race, education levels, gender and socio-demographics, though they certainly play a role in cancer incidence worldwide. It is no secret that public awareness, investigations focusing on lifestyle interventions and cancer outcomes, patient education, and screening campaigns are ways to combat the affliction with PC.

1.4.2. Race

Race has been linked with increased PC cancer incidence and mortality.[33] Though the meaning of race is unclear, it is frequently used in the literature to describe a social construct with biological implications.[26] To this end, race has been linked with socially-derived, hierarchical classification systems based on one's skin pigmentation which individuals use to associate themselves culturally, religiously, physically and politically.[34, 35] Race differs from ethnicity, which refers to groups of people from a similar nation-state. Biologically, race refers to one's distinct ancestry, origins, and family history.[36]

In general, the body of literature that specifically looked at race influencing the outcome of prostate biopsies, whether initial or repeat, is mixed. Potts et al, for example, investigated the relationship between PSA and race retrospectively over a sixteen-year period and found that there was no association between race and cancer outcome. They did find, however, that cancer was found more frequently in blacks than whites, though the association diminished when controlling for PSA.[22] Additional studies by Grunkemeier et al and Yanke et al, both prospective studies that employed new modeling nomograms, were inconclusive on the topic of race and cancer diagnosis, but validated PSA as a useful tool for screening, suggesting that looking at PSA and race together could prove to be a predictive tool in diagnostic outcomes.[37, 38] The literature suggests

that given baseline characteristics race alone may not be a valuable tool for prognostic predictions on an individual patient level. The inconsistencies in the crude data compared with the adjusted data have resulted in conflicting results: some literature sources say race alone could be predictive of outcome, others, only when stratified by effect modifiers.[39] Therefore, the ability to establish an alternative diagnostic tool that incorporates race as the primary focus, which will help clinicians determine, pre-biopsy, whether a patient will present with cancer on biopsy, is needed. In order to eliminate race as a "health disparity" related to PC incidence, more studies are required to evaluate whether race is a predictor of PC on biopsy and the underlying biological cause of the differences seen in epidemiological studies focused on health disparities.

1.4.3. Education

Education is the most commonly used indicator of socioeconomic status used in public health studies.[40] While a marker for current and future earnings, education represents a multifaceted concept, which is hard to measure in empirical, epidemiological studies.[41] More than just how much formal schooling one has received, deriving a definition of education as it pertains to health status, health seeking behaviors and health outcomes is challenging. Education also must include health literacy and communication, overall literacy, and knowledge of health related matters.[42] Unfortunately, most studies, when including education in models as a representation of socioeconomic status, do not specify

which of these components is being measured, therefore understanding the underlying relationship between education and socioeconomic status as well as education and health outcomes is unclear.[40] In order to fully understand which facets of education as a marker of socioeconomic status are being discussed, better data with more specific variable, or combination thereof, must be included in the research in order to fully understand risk outcomes.[43, 44]

1.4.4. Access

Access to care, one of the pinnacles of health disparities research, encapsulates more than whether or not one can receive the right care at the right time for the right health condition.[45-47] Access to care, inclusive of access to screening for chronic illnesses, can refer to whether or not individuals can come into contact with the healthcare system and utilize its benefits, physically (i.e. distance to care facilities), financially (i.e. insurance status, qualifications for care), and knowingly (i.e. having the ability to make informed decisions about their health). Access can also reference whether or not primary care gatekeepers are available to help patients maneuver within the system to get the care and tests they need with appropriate care providers eligible to provide that care. In general, patients with lower socioeconomic status are less likely to come in contact with the health care system in general[48]; specifically, they have less access to primary care providers and

specialists, less education to know how to make informed decisions[49] and maneuver within the system once they do manage to encounter it, and overall worse outcomes.[50]

1.5. Research Objectives

The goal of this thesis is to examine the effects of selected health disparity constructs on PC risk and aggressiveness among men undergoing initial prostate diagnostic and screening procedures. In particular, in an American population where racial disparities embody a significant portion of the health disparities encountered on a population-level, in our first study we examined the association between race and having cancer on initial biopsy, and for men who had cancer, the grade of their tumors at initial biopsy. We hope to understand at what diagnostic point a man's race, a construct which encompasses biologic and socioeconomic aspects, plays a role in disease outcome.

Given a lack of general Brazilian PC data, there is even less information available on screening and PC specific mortality. Our second study seeks to close the gap by providing insight into barriers faced by underprivileged men who seek PC screening as measured by socioeconomic constructs and PC outcomes. Therefore, we examined the distance between the initial mobile medical unit screening site to BCH, hypothesizing that men at greater distance from the hospital are less likely to comply with biopsy

recommendations and follow through with biopsy. Furthermore, we hypothesized that these men who live farther away would be at an increased risk of having more aggressive cancer. In an additional analysis, we examined the association between education and risk of noncompliance with recommendations to have a biopsy, having cancer on biopsy and cancer aggressiveness. Thus, through this study we hope to address issues of access to health care, and education level as a means to explore and better understand PC prevention and diagnosis problems in underserved areas of rural Brazil.

In pursuit of these goals, two populations of men were identified with complete data and appropriate baseline clinical characteristics to better understand the effects of these constructs in respective developed and developing countries from which they stem. Therefore, our approach consisted of the following:

Objective 1: Evaluate the role of race in PC risk and aggressiveness among men undergoing initial prostate needle biopsy in an American multiethnic, contemporary, equal-access hospital.

Objective 2: Evaluate the roles of educational attainment, distance from screening site to follow-up care facility, and their interaction with risk of noncompliance, PC risk and PC aggressiveness among men undergoing initial prostate screen and subsequent biopsy in

rural and urban municipalities in Southern Brazil. These men were screened off-site on medical mobile units in their towns and referred for follow-up at a single-site equal access hospital.

2. Methods & Study Design

2.1. Durham VA Study

2.1.1. Data Collection

After obtaining institutional review board approval, we conducted a retrospective review of 1,277 men who underwent an initial prostate needle biopsy between 2001 and 2009 at the DVAMC. Enrollment methods have been described previously[51]. Participants were referred for biopsy through the urology clinics typically due to elevated PSA ($\geq$ 2.5 ng/mL) or abnormal DRE findings. Participants who qualified were then encouraged to schedule a biopsy. Upon returning for their biopsy, a repeat pre-biopsy PSA test was performed to confirm indication.

2.1.2. Study Population

We excluded 19 men who were missing data on race or whose race was neither black nor white. Men missing data on pre-biopsy serum PSA (n=43), DRE (n=127), BMI (n=88), total number of biopsy cores (n=112), and Gleason score (n=1) were also excluded from analysis, resulting in a study population of 887 subjects (69.5%) available for analysis.

2.1.3. Data Analysis

From participant records, we extracted age at biopsy (years, continuous), race (self-report, categorical), BMI ($\leq$24.99, 25 – 29.99, 30 – 34.99, $\geq$ 35 kg/m^2, categorical), DRE (dichotomous, normal/abnormal), pre-biopsy PSA (continuous, ng/mL), prostate volume

(continuous, cm^3), year of biopsy (continuous, 1994-2009, years), total number of biopsy cores (continuous, range 1 – 24 cores), total number of biopsy cores that were positive for cancer (continuous, range 0 – 15 cores), and biopsy findings (benign vs. cancer, and Gleason score, if cancer positive).

Race, our primary exposure variable, was based on self-report. From the unrestricted dataset (n=1,277), men identified as 1=black (n=614, 48.1%), 2=white (n=644 50.4%), 3=Asian (n=0, 0%), 4=Hispanic (n=2, 0.2%), 5=other (n=9, 0.7%) or had race data missing (n=8, 0.6%). Due to small numbers in the other racial groups, we restricted our analysis to include only black and white men. As no ancestral marker data was available to confirm racial identity, we assigned the men to their respective racial groups based upon their primary classification. In this case, race was converted from a five-level categorical variable, to a dichotomous variable called "black1" coded as 1=black, 0=white. Analyses inclusive of all racial groups did not materially change the strength of the association of race as a predictor of PC on initial biopsy; therefore, excluding the other racial groups did not have a strong effect on our data and subsequent outcomes.

Pre-biopsy PSA, which was extracted directly from patient records, was evaluated in models after being logarithmically-transformed. As this study was recruited on a rolling basis, there are no data available for the amount of time that lapsed between the initial

abnormal prostate screen via PSA test (and what those values were) and the pre-biopsy PSA test that was administered the same day patients received their biopsy. As the PSA range from patients included in this study was from 0.30 – 342.6 ng/mL, we evaluated the variance, skewness and kurtosis of the data to determine if it was normally distributed based on the wide variety observed. We determined, based on these values (variance: 27,751.79; skewness: 15.93; kurtosis: 287.47) that our variable was not normally distributed and therefore required logarithmic transformation before inclusion in our models. Unfortunately, there is no clinical use for "logpsa", therefore, values for baseline clinical characteristics were determined prior to changing our variable and only used in models evaluating risk of cancer and risk of cancer grade. For these analyses, we did not include measures of PSA in our models because PSA is used to detect PC and therefore is intricately linked with PC risk.

Participants' BMIs (kg/m^2) were calculated from height and weight measurements obtained at the time of biopsy and abstracted from medical records. On a population level, black men are more likely to have higher rates of obesity and obesity-mediated illnesses than white men.[52, 53] With respect to PC, BMI is a known risk factor as studies have linked increased BMI with increased PC risk.[54] This increased PC risk could be due to hemodilution[55], a phenomenon wherein more obese men have lower PSA readings at diagnosis due to blood volume dilution, therefore, increasing risk of delayed detection

and decreasing risk of early detection, resulting in more aggressive cancer when actually diagnosed, or having a smaller prostate gland.[56, 57] For our data, we elected to evaluate BMI categorically based on classifications used in clinical practice rather than as a continuous variable as there is no evidence that for every unit of BMI increase, there is an equivalent change in risk of PC.

In this dataset, DRE was coded dichotomously as 0=normal, 1=abnormal from data pulled directly from patient records. For our analyses, we were interested in the subset of men whose DRE was "abnormal", a predictor and indicator of PC and PC risk. One potential issue with DRE in PC detection pertains to evaluating who has a normal vs. abnormal DRE. DREs are subjective and are subject to provider opinion, having a positive predictive value of 8.8%[58]. Different providers may evaluate men differently and have different thresholds for characterizing a DRE as abnormal. One way to verify DRE accuracy is by using transrectal ultrasound, however only a small portion of men in our study received these measures of prostate volume, and this measure was not included in analysis.

Data for the total number of cores taken at biopsy and the total number of cores positive for cancer were derived directly from pathology reports included in patient medical records. Additional classifiers, such as percent of each positive biopsy core that had

cancer, were also available for evaluation. We elected not to use percent cancer in our analysis due to collinearity with total number of cores positive for cancer (correlation coefficient, $r=0.98$, $p<0.001$) and lack of epidemiological relevance. Furthermore, as the average number of cores obtained increased steadily over the total timeframe from which the entire dataset – inclusive of our subset – was collected (1994 – 2009), we did not include the year of biopsy in our multivariable model due to collinearity with total number of biopsy cores (correlation coefficient, $r=0.59$, $p<0.001$). We evaluated total number of cores and total number of cores positive continuously given clinical standards to take approximately twelve cores per biopsy patient, a change that occurred from sextant biopsy standards around 2001. To standardize our analyses, we evaluated only men who received biopsies between 2001 and 2009 to ensure that there were no differences in the risk of cancer between men who received a sextant-core biopsy, and those who received a twelve-core biopsy.

Given that larger prostate glands produce larger quantities of PSA in both benign and malignant prostates, studies have shown that prostate volume is a known predictor of PC risk when the PSA test is used in screening as cancer causes increased production of PSA.[59] While the argument could be made that prostate volume is on the causal pathway for PC detection, because benign prostatic hyperplasia and prostatitis are also clinical conditions in which cancer is not present and increased PSA levels are obtained, there is

no definitive link between prostate volume and PC alone. Clinically, men with smaller prostates who are at risk of cancer have a higher likelihood of having cancer detected on biopsy.[60] Conversely, men with larger prostates are more likely to have some of their cancer missed on biopsy, resulting in fewer positive cores and a skewed view of their cancer grade.[61] As such, we elected to investigate models that both included and excluded controlling for prostate volume. Subanalyses for men including prostate volume and complete data were performed to evaluate the role of PC risk in our models. Though at baseline, black men were found to have smaller prostates than white men (data not shown), the addition of prostate volume in our model did not materially change the strength of the association between black race and PC risk. Unfortunately, complete data including prostate volume were unavailable for the majority of men (n=456, 51.4%) and therefore was not included in the final analyses.

Our primary and secondary outcomes were cancer risk on initial biopsy and cancer grade. Cancer risk on initial biopsy was derived from medical record pathology reports, which indicated whether or not patients had cancer on their initial biopsies. Cancer grade was defined as no cancer (reference group), low-to-intermediate risk cancer (Gleason Score <7) and, high-risk cancer (Gleason Score ≥ 7).[62]

2.1.4. Statistical Design

Continuous baseline clinical and demographic characteristics (age, year of biopsy, total number of biopsy cores, prostate volume, pre-biopsy PSA) were compared between black and white men using the Wilcoxon rank-sum test. Categorical variables such as DRE (normal/abnormal) and BMI (<25, 25–29.9, 30–34.9, and ≥35 kg/m^2) were compared using the chi-squared test.

We evaluated the risk of PC diagnosis by race using both crude and multivariable logistic regression models (effect measure estimates odds ratios [OR]). In secondary analysis, we assessed the association between race and cancer grade (low-grade Gleason <7 vs. no-cancer, high-grade Gleason ≥7 vs. no-cancer)[62] using a multinomial logistic regression analysis to accommodate the three levels of the outcome variable (estimates relative risk ratios [RRR] not OR). In both cases, multivariable analyses were adjusted for age, BMI, total number of cores, PSA (logarithmically-transformed), and DRE. Although our preference was to report RRR and not a combination of OR and RRR to maintain conformity amongst our results, adjusted binary generalized models used to estimate RRR did not converge, thus two effect measures are reported.

To determine whether or not there were changes in the association between race and cancer risk and grade and restricting our cohort based on biopsy scheme changes, we

evaluated models, which restricted the years of biopsy to 2001 through 2009 and the full cohort, 1994 through 2009. In these models, we also looked at controlling for PC risk predictors PSA and DRE. While adding the covariables PSA and DRE to the models did have an impact on the association between race and cancer grade and cancer risk, restricting the analyses based on biopsy year did not. Given the changes in biopsy schema, we therefore elected to evaluate the subset of men who were more likely to receive twelve-core biopsies than those of the previous sextant era given the increased likelihood to detect cancer and given that six-core biopsies are no longer used in practice. We also elected to remove PSA and DRE adjustments from analysis because they cofounded the relationship between race and cancer as they are used in cancer detection and those with higher PSAs and abnormal DREs are most likely to have cancer on biopsy.

All statistical analyses were performed using Stata 12.1 (StataCorp, College Station, TX, USA). Two-tailed p-values of ≤ 0.05 were considered statistically significant.

2.2. Barretos Cancer Hospital Screening Study

2.2.1. Data Collection

After obtaining institutional review board approval, we conducted a retrospective review of 17,573 medical records from men undergoing initial PC screening from 2004 to 2007 in 231 underprivileged cities in Southern Brazil. [54, 55] PC screening took place on medical

mobile units based out of BCH. Screening location was targeted to a specific geographic region in which the cities tended to be of low socioeconomic status. Specific enrollment methods have been described previously.[63, 64] Study participants received PC screens from mobile medical unit personnel by on-site prostate specific antigen (PSA) testing and digital rectal exams (DRE). Men with an elevated total PSA (tPSA) over 4.0ng/mL, tPSA between 2.5 – 4.0ng/mL with percent-free PSA (pfPSA) $\leq$15%, or with a DRE suspicious of PC, were contacted by mail or phone and referred to BCH for follow-up. Once at BCH, indications were confirmed with another PSA test and an additional DRE. Men whose indications were confirmed were referred for biopsy though we do not have data for the amount of time between the date of the initial screen and when the men presented to BCH for follow-up testing and biopsy.

2.2.2. Study Population

We excluded men who had previously been screened, biopsied or who had cancer (n=6,456) and men who were missing data on education (n=6) or PSA (n=644), leaving a resultant population of 10,467 (60%) men. Of these 1,561 (9%) men were referred for biopsy and 1,131 (73%) complied with the recommendation and 430 (27%) did not comply. Reasons for noncompliance include men not attending the initial screen (n=375), attrition (n=43), they elected to be followed by a primary care physician (n=5), they refused to proceed with biopsy (n=6), or for other reasons not specified (n=1). Of the

1,131 men recommended to have a biopsy who complied, 273 men were excluded from analysis because they did not have a biopsy upon reporting to BCH as requested. Reasons for not having a biopsy include a change in biopsy indication upon reporting to BCH (n=81), they presented for biopsy outside of the screening interval (n=60), they had a PSA too low to be suspicious of PC (n=131), or they were waiting for the procedure (n=1). Further, 8 additional men were excluded from analysis due to missing Gleason score or pathological clinical stage post-biopsy. Therefore, for secondary and tertiary analyses evaluating cancer on biopsy and cancer grade, respectively, 850 (5%) men were included for analysis.

2.2.3. Data Analysis

Among all screened men, we extracted age at screening (continuous, years), tPSA (continuous, ng/mL) at screen, distance from screening site to BCH (categorical, <250, 250-500, 500-1000, ≥ 1000 km), maximum level of educational achievement attained, family history of PC (dichotomous, yes/no), family history of any cancer (dichotomous, yes/no), calendar year of screening (categorical, 2004, 2005, 2006, 2007), DRE findings (dichotomous, normal/abnormal), and biopsy criteria from medical mobile unit patient medical records. These records were forwarded to BCH for men recommended to biopsy where their PSA and DREs were repeated prior to biopsy for confirmation of screening findings. Of the men who received biopsies, in addition to the aforementioned data, we also extracted cancer grade using Gleason score (categorical, low-grade=2-6,

intermediate=7, high-grade=8-10), pathological clinical stage at biopsy (categorical, Stages 1-4), total number of biopsy cores taken (continuous, range 10 – 14), total number of positive biopsy cores (continuous), prostate volume (continuous, cm^3), tPSA at biopsy (continuous, ng/mL), biopsy findings (categorical, benign vs. low/intermediate-grade cancer vs. high-grade cancer) and transrectal ultrasound results (TRUS, categorical, normal, hyperechoic nodules or hypoechoic nodules).

Age was collected from medical records based on patient report at the time of screening. We evaluated age continuously as the data were normally distributed. For the full dataset (n=17,573), the age range was 45 – 98 years. For the subset of men included in compliance analysis (n=1,561), the age range was 45 – 92 years for those who complied to biopsy recommendations (n=1,131), and 45 – 94 years for those who did not (n=430). Of the men who had a biopsy (n=850), the age range was 45 – 92 years, as well. Given the established relationship between age and PC incidence, we decided to capture both the full spectrum of the age-PC relationship (unrestricted), as well as examine any differences that may be seen by mimicking the subset of men who would be most likely to be screened here in the US (restricted). To capture the most number of men in the restricted dataset, we evaluated men 50 – 82 years old. We selected 82 years as the upper limit to be inclusive of the majority of men. Thus, we evaluated crude and multivariable models of cancer on biopsy and cancer grade using restricted (50 – 82 years, n=829, data

not shown) and unrestricted age ranges (45 – 92 years, n=850) and determined that in this data set, there were no differences in the model outputs by using restricted or unrestricted age as a covariable.

DRE status and PSA were used as the main diagnostic predictors of PC in this cohort. DRE status was evaluated based on biopsy criteria and DRE findings. A combination dichotomous new variable was created to assess whether the DRE was truly suspicious of PC or not. We elected to use pfPSA, tPSA and fPSA measures to justify recommendation to biopsy for men presenting for screening based on PSA findings in our cohort. For associations between non-compliance and PSA, we logarithmically-transformed the values for tPSA to obtain a normally distributed continuous variable for analysis.

Educational status, one of our predictors of compliance, cancer on biopsy and cancer grade, was coded as a five-tiered categorical variable as follows: illiterate, incomplete primary school, complete primary school, high school and college. Only six men in the entire cohort were missing data on education. When evaluating men who had received a biopsy, we combined the two highest education categories, high school and college, into one because of the small number of men in these groups. This new category was indicated “high school + college” and was used in the models that examined the relationship between education and having cancer on initial biopsy. On tertiary analysis

looking at cancer grade, the small sample size of the higher education group prohibited analyses to be completed in the high-grade cancer groups, also a result of small sample size of this group. To account for this fact, a dichotomous variable stratifying educational status based on low (illiterate and incomplete primary school) and high (complete primary school, high school and college) educational attainment was created and used to evaluate the association between educational attainment and cancer grade. Additionally, to evaluate the interaction between education and distance on cancer risk and cancer grade, a new variable, educ*dist, was generated as the cross product of the five-level categorical education variable multiplied by the categorical distance variable. This interaction term was used to evaluate the relationship that distance and education have collectively on cancer risk and cancer grade among men undergoing initial prostate biopsy.

Compliance, our primary outcome measure, was evaluated based on whether or not men adhered to their recommendation. We based the coding of this variable on whether or not the men were recommended to biopsy and whether or not their biopsy was cancelled. Biopsies could be cancelled for the following reasons: (1) presented for biopsy outside the screening interval; (2) lost to follow up; (3) recommended to be followed through a primary care center; (4) refusal of biopsy; (5) biopsy indication was changed at BCH; (6) PSA was too low to be suspicious of PC; (7) awaiting the biopsy procedure. Thus,

compliance was defined as: compliant = 3, 5, 6, 7, and non-compliant = 1, 2, 4. Associations between predictors of compliance and compliance between those men who complied and those who didn't were evaluated using rank-sum test for categorical variables and chi-squared test for continuous variables.

Our secondary and tertiary outcomes, cancer risk on initial biopsy and cancer grade, were evaluated using two cancer outcome variables. Cancer risk on initial biopsy was derived from medical record pathology reports, which indicated whether or not patients had cancer on their initial biopsies. Cancer grade, the tertiary outcome, was defined as no cancer (reference group), low-to-intermediate risk cancer (Gleason Score <7) and, high-risk cancer (Gleason Score $\geq$ 7).[62]

2.2.4. Statistical Analysis

Categorical baseline clinical and demographic characteristics such as distance, educational status, calendar year of screening, family history of any cancer, family history of PC, and DRE suspicious of PC (yes/no) were compared using the chi-squared test. Continuous variables such as age and tPSA were compared using the Wilcoxon rank-sum test. These comparisons were evaluated among all men who presented for initial PC screen. Additionally, we stratified these men based on each evaluation time-point of recommendation status and compliance (all screened men, men who were

recommended for biopsy, men who were recommended for biopsy and complied with their biopsy recommendation, men who were recommended for biopsy and did not comply with the recommendation, and men who had a biopsy). We used a chi-squared test to determine the differences between men who complied to biopsy recommendations and those who did not to determine differences among risk factors for compliance to biopsy recommendations.

To evaluate characteristics of the men who received a biopsy, we performed a secondary analysis of baseline clinical characteristics and demographics stratified by educational attainment. Continuous clinical characteristics age and tPSA were evaluated using analysis of variance test (ANOVA) across the four educational categories. Categorical variables distance, calendar year of screening, DRE status, family history of any cancer, and family history of PC were compared using the chi-squared test. Similarly, to describe cancer outcomes of those men who received biopsy at BCH, clinical descriptive statistics such as cancer status, Gleason score, clinical stage, TRUS findings, total number of cores taken at biopsy, total number of cores that were positive for cancer taken at biopsy, prostate volume, and tPSA at biopsy results were examined.

We evaluated the risk of non-compliance to biopsy recommendations and PC diagnosis on initial screen by educational status, distance to BCH, and the interaction between

education and distance using both crude and multivariable logistic regression models (effect measure estimates odds ratios [OR]). On secondary analysis, we assessed the association between educational status, distance to BCH and cancer grade (low-grade Gleason <7 vs. no cancer, high-grade Gleason ≥7 vs. no cancer) using a multinomial logistic regression model to accommodate the tri-level outcome variable. In this case, the model used estimates of relative risk ratios [RRR] not ORs. The final models were built by singular addition of selected outcome predictors sequentially from the unadjusted model to the multivariable model using forward stepwise addition. Assessments of which variables to include in the final models were based on the fewest required adjustments to the model. This decision was made considering the amount of change in effect measures from the crude model to final model and its associated p-values. As indicated, refined models include an adjustment for the interaction term. Final multivariable models have dropped this term out based on associated p-value findings of the interaction term in the refined models. Additionally, in multivariable models associated with cancer risk or cancer grade, we elected not to adjust for tPSA, DRE or prostate volume because these variables are diagnostic indicators of PC, potential confounders, and reside on the causal pathway predicting risk. All statistical analyses were performed using Stata 12.1 (StataCorp, College Station, TX, USA). Two-tailed p-values of ≤0.05 were considered statistically significant.

3. Durham VA Study: Race & Prostate Cancer Risk on Initial Biopsy (Manuscript 1)

3.1. Introduction

In Western society, PC is the most frequently diagnosed non-skin malignancy in men, with black men twice as likely to die from PC as white men.[12] The increased risk of aggressive disease could be due to increased risk of having cancer on biopsy, higher risk of aggressive disease at diagnosis, poorer outcomes after treatment, or a combination thereof.

Regarding outcomes after treatment, the data are mixed as to whether race is correlated with poor outcomes.[65-67] However, a key question is whether adjusting for stage, grade, and other clinical parameters (i.e. "all else being equal") can explain the worse outcomes in black men. One approach to accomplishing this uses data from an equal access medical center, wherein differences in access to care are minimized and detailed clinical characteristics are available and can be accounted for. We have previously shown in an equal access setting that black men are more likely to have a prostate-specific antigen (PSA) recurrence after radical prostatectomy even after controlling for clinical characteristics[68], supporting the hypothesis that black race is linked with PC aggressiveness.

There are two possible non-mutually exclusive ways that black men could have more aggressive disease: increased risk of having cancer on biopsy (i.e. higher incidence) or increased risk of aggressiveness of the cancer. While on a population level, black men do have increased PC incidence, this does not address the "all else being equal" (i.e. controlling for confounders). In contrast to the consistent population level data showing increased PC incidence in black men, individual studies show mixed results as to whether black race is a risk factor for PC at the time of biopsy.[69, 70] Similarly, studies examining the aggressiveness of the cancer as a function of race have been inconclusive.[71, 72]

We examined the association between black race and biopsy outcomes in men undergoing initial prostate biopsy at the DVAMC. We hypothesized that black race is associated with PC aggressiveness and postulated that when all else is equal, black race will be associated with increased PC risk and disease severity.

3.2. Results

3.2.1. Baseline Clinical Characteristics

There were similar proportions of black (n=431, 48.6%) and white men (n=456, 51.4%) in this cohort. Black men were younger at biopsy (median age: 61 vs. 65, $p<0.001$, Table 1) and had higher pre-biopsy PSA values (6.6 vs. 5.8 ng/ml, $p=0.001$). A smaller proportion of black men had abnormal DRE findings than white men (25.3% vs. 30.9%,

p=0.06), though the difference was not statistically significant. There were no differences between black and white men in BMI (p=0.32), total number of biopsy cores (p=0.84), or year of biopsy (p=0.29).

In our data set, among men under 55 years old (n=115), 81 (70.4%) were black, and 34 (29.6%) were white. In this subset, black men still had higher pre-biopsy PSA (black, median [IQR]: 5.5 [4.4–8.5]; white, 5.1 [3.1–6.6]) than their white counterparts.

3.2.2. Biopsy Outcomes

Of the 887 men, 499 had cancer on biopsy (56.3%, Table 2). Black men (61.9%) were significantly more likely to have cancer on biopsy than white men (50.9%, p=0.001). Among men with cancer, there was no significant evidence that black men had more positive cores than white men (p=0.08). Of the men with a positive biopsy, high-grade PC was more common in black men than in white men (54.3% vs. 46.9%), although the difference was not statistically significant (p=0.10).

In our data set, among men under 55 years old, a greater proportion of black men still had cancer (black 60.5% vs. white 47.1%) though there were no differences in the clinical characteristics among men with cancer between blacks and white (p=0.12 for PSA, p=0.17 for biopsy outcomes).

To evaluate whether our results were confounded by prostate volume, we examined a subset of men with available prostate volume data (n=489, 49%). Among men in this subset similar to the entire cohort, race was significantly related to PC risk on multivariable analysis (OR 1.48, 95% CI 0.99 – 2.20, p=0.058). The addition of prostate volume to the multivariable model did not materially change the strength of the association between race and biopsy.

3.2.3. Crude Associations Between Race and Cancer

On crude analysis, black race was associated with a significantly increased risk of PC on biopsy (OR: 1.57, 95%CI: 1.20–2.05, Table 3). When stratified by grade, on crude analysis, black race was more strongly linked to high-grade (RRR: 1.82, p<0.001) than low-grade PC (RRR: 1.35, p=0.06, Table 3), as compared to the 'no cancer' category.

3.2.4. Adjusted Associations Between Race and Cancer

The association between black race and risk of PC on biopsy changed minimally after adjusting for age, total number of cores, BMI, DRE and PSA (OR: 1.50, 95%CI: 1.12–2.00, Table 3). After multivariable adjustment, race was not significantly associated with low-grade PC (RRR: 1.29, p=0.14), but remained significantly associated with high-grade PC (RRR: 1.84, p=0.001, Figures 1,2).

In our dataset, among men under 55 years old, multivariable logistic regressions for cancer on biopsy (OR: 1.44, 95%CI: 0.62–3.37, p=0.40), and multivariable multinomial logistic regression analyses (relative to no cancer, low-grade: RRR: 1.23, 95%CI: 0.47–3.21, p=0.676, high-grade: RRR: 1.99, 95%CI: 0.60–6.59, p=0.261) suggested positive associations between race and cancer, and race and cancer grade in this subset, though the associations were not statistically significant.

3.3. Discussion

Accounting for almost 10% of cancer deaths in American men, PC remains the most prevalent form of cancer in men with an estimated 238,590 new cases diagnosed in 2013.[73] This burden is highest among black men. Whether this can be explained by inadequate access to care remains unclear. As such, our key finding that in an equal access setting with analyses adjusted for baseline clinical characteristics, black men have an increased risk of PC on initial biopsy, specifically high-grade PC, supports the hypothesis that black race is inherently linked with more aggressive PC.

Overall data on whether race predicts PC after adjusting for clinical characteristics are mixed. The magnitude of the positive association between black race and increased PC risk (50% increased risk) is consistent with that of population-level findings from both SEER (67% increased risk) and the Prostate Cancer Prevention Trial (40% increased

risk).[12, 74] Although the association between black race and increased PC risk is well-documented, several studies found that race is not a predictor of PC risk in populations on repeat biopsy,[75, 76] or in men who had fewer than 12-biopsy cores taken[70]. Such findings suggest that selection bias may have an effect on PC risk in these populations. Furthermore, one study found that race was not associated with increased PC risk when adjusting for socioeconomic status and literacy. However, the study may have lacked power to detect a significant association due to a small sample size (n=212).[77] Collectively, while these studies all suggest that race is not an independent predictor of PC risk, none also looked at the association between race and PC grade or controlled for other factors that may influence risk on initial biopsy.

To our knowledge, our study is the first conducted in a contemporary cohort to confirm that black race is an independent predictor of total and high-grade PC on initial biopsy. Yanke et al, for example, examined race as a predictor of cancer on initial biopsy with a cohort of almost 10,000 men from three different equal access care centers; however, they did not include analyses evaluating cancer grade as an outcome of their predictions.[69] Our results are consistent with their findings. While results from this study support the idea that black men should be targeted more aggressively for initial PC early detection efforts, one notable feature of our cohort is that the DVAMC is an equal access hospital, which minimizes the effects of access to care issues. Therefore, by making

everything equal to the extent possible in our study, the fact that black men were still at an increased risk for PC overall and, specifically for high-grade PC, points to a need for additional studies aimed at understanding the molecular underpinnings for this phenomenon. Likewise, it suggests that more rigorous screening for PC in black men could be beneficial.

While there has always been controversy surrounding the benefits and risks of PSA screening, this has intensified recently with the publication of the U.S. Preventive Services Task Force (USPSTF) guidelines on PSA screening and the American Urological Association (AUA) guidelines on PC screening. Specifically, the USPSTF suggests the risks of PSA screening outweighs the harms[78], while the AUA suggests shared decision making, but only for men between the age of 55 and 69.[79] Notably, the AUA guidelines discuss recommendations for men at "average risk" of PC. However, based upon the current data and those of others, it is clear that black men are not average: they have greater than average risk. As such, what policy should be developed for screening within a group that is clearly at high-risk for aggressive PC and PC death?

While one could argue that such a group is in most need of screening and early detection, a counter argument could be made that given the inherent aggressiveness of PC in black men, that screening would be unable to overcome this. In support of the former

argument, it should be noted that during the PSA era, PC deaths declined to a greater extent in black men than white men[73]. As such, this provides circumstantial evidence that screening is beneficial for black men. Indeed, the goal of screening is to identify men at greatest risk of PC death who in theory stand the most to benefit. The current data suggest that black men represent such a group. Therefore, if further studies support our findings that even at initial diagnosis, black men present at younger age and with more aggressive disease, this would strongly support targeted screening approaches for all men of African ancestry – even below the AUA guidelines age limits of 55.

In our analysis of men younger than 55 years, there were a larger number of black men, they had higher PSA levels, and, relative to white men, had more aggressive cancers. While an association between race and cancer on biopsy and race and cancer grade is evident, there were no statistically significant associations in these models, which could be the result of small numbers and low power within men in this subset with complete data from our dataset. Thus, while this subset analysis does not show that early and aggressive screening helps black men it still provides evidence that, in conjunction with population-level data, screening younger black men will identify more cancers at an earlier stage, which is a pre-requisite for screening to improve outcomes.

As with any retrospective study, there are limitations regarding the outcomes reported and generalizability investigated here. With respect to our population, our cohort is not representative of the general U.S. population as we are analyzing data from veterans using an equal access facility**.** Because we had access to data from a single equal access facility, our sample size is relatively small. Additionally, exclusions are high, as the data were not uniformly collected for all patients, though similar trends were noted in men who did not have complete data available for analysis. Even though zip codes are recorded in medical records, we did not have complete data available and were unable to separate the effects of race from socioeconomic status. Some data suggest that even when controlling for socioeconomic factors, black race remains an independent predictor of disease recurrence and/or cancer mortality[80]. Furthermore, family history data was not available for men included in this cohort. Of significance is that in this study, race was self-reported, given the heterogeneity of ancestral marks among self-reported blacks. As a result, important social and cultural structures may not be controlled for or measured that influence results. Future studies should examine the combination of ancestral markers, genetic mapping, and ethnicity to determine the exact relationship between genetic racial identification, social racial identification, and adherence to cultural norms with respect to cancer predictability on biopsy. Given that genetics only accounts for approximately 5- 42%[81] of the biological differences between races, it is clear we need to

develop a better understanding of the non-genetic drivers of racial differences as it relates to PC risk.

A strength of this study is that DVAMC is an equal access facility which should minimize health care access issues among those qualified to receive care at this facility.[82] Additionally, though also described as a limitation, in this context, self-reported race lends insight into the cultural and social indices that people use to self-identify and provides valuable insight beyond mere genetics. It is clear that race is not the biological classification strata historically represented in research and other studies, thus further studies to fully understand the link among black race, PC risk, and PC tumor aggressiveness are needed.

3.4. Conclusion

In an equal access medical center, we found that black race was positively associated with an increased risk of overall and high-grade PC risk on initial prostate biopsy even after adjusting for key clinical characteristics. This suggests that when all else is equal, black men are at a heightened risk for PC, which should be taken into account when considering whether to screen black men given current PC screening guidelines are based on average risk men.

4. Barretos Cancer Hospital Study: Education, Distance, Compliance to Biopsy Recommendations & Prostate Cancer Risk on Initial Biopsy (Manuscript 2)

4.1. Introduction

Brazil is the largest country in South America and home to a plethora of population groups and diverse environmental regions marked by extreme disparities, both socioeconomically and with respect to health-care access.[83] Cancer is the third leading cause of mortality, accounting for nearly 72% of the chronic, non-communicable disease mortalities in 2007.[84.85] Among Brazilian men, PC is the most diagnosed cancer with incidence rates that are steadily increasing.[86] This increased PC burden is likely due to increased screening.

Like many underprivilidged areas, screening for PC in Brazil is not without its challenges. As a developing country in transition with cancer registries still solidifying, data is sparse regarding predictors of cancer, cancer mortality, and cancer outcomes. To date, there is very little research on the effects of risk factors, ineffective screening and access to health care in these and other Latin American communities with regard to PC. A beginning step toward managing what is now finally being recognized as a serious public health concern, officials have recognized the significance of the burden of cancer, both socially and economically, and are doing what they can to extend as many lives as

feasible. The use of a single-site tertiary-care facility to cater to rural and nearby urban populations has been proposed to spearhead screening efforts to reach rural populations that have limited access to follow-up care. Though from a data perspective this will help unify collection efforts, geographic distance from screen site to the centralized hospital may prove to be a barrier for men undergoing screens who live far away. These challenges with respect to obtaining adequate follow-up, for example, obtaining transportation due to a lack of public transit, loss of daily wages, climate barriers, and inadequacy of local health facilities, still exists.[87, 88]

Educational level has been reported to be associated with health outcomes and mortality in countries with higher average educational levels.[89] Thus, educational achievement among men in rural areas may be a barrier to PC screening as well. As men in rural areas have less access to higher education, these men are at increased risk of having low overall and health literacy levels, and specifically, little knowledge about PC, its symptoms, and treatments. Thus, low education is a marker for low socioeconomic status and therefore increased risk of health disparities. Though the relationship between literacy levels and screening has been examined[90], the link between literacy levels and PC-specific outcomes has been untested in these populations. As such, the exact relationship, if any, among education, geographic distance to care, and compliance with PC risk is unknown. We seek to examine whether education is associated with health outcomes and behaviors in a

setting where the average educational level is very low, especially relative to US educational standards.

We examined the relationship between noncompliance to biopsy recommendations among all men recommended to biopsy with educational status and distance from screening site to follow-up care center. As a secondary analysis, among all men who complied with biopsy recommendations and had a biopsy, we evaluated the association between educational status, distance from screening site to follow-up care center and biopsy outcomes in men undergoing initial prostate screen and subsequent prostate needle biopsy at BCH. We hypothesized that lower educational status, greater distance from screening site to follow-up care center, and the interaction thereof would be associated with increased risk of noncompliance to biopsy recommendations, overall PC risk and disease severity.

4.2. Results

4.2.1. Baseline Clinical Characteristics

Non-compliant men (n=430, 27.5%) were older at initial screen (median: 68 vs. 66 years, $p<0.001$), had higher tPSA results (median: 4.90 vs. 4.2 ng/mL, $0<0.001$), and were less likely to have an abnormal DRE (19.5% vs. 33.4%, $p<0.001$) when compared to men who complied with biopsy recommendations (n=1,131, 72.5%). Socioeconomically, non-

compliant men had less education (low education: illiterate + incomplete primary vs. high education: complete primary + high school + college, 1,402 vs. 159, p=0.14) and were more likely to live more than 500km from BCH (66.3% vs. 19.6%, p<0.001). There were no differences in family history status for any cancer (p=0.07) or for PC (p=0.15) among all men recommended to biopsy (Table 4).

The overall education level of the population of men who presented for biopsy was low. Stratified by education, there were fewer men in the higher educational groups, high school, college and complete primary school (n=84, 9.8%), than those in the lower groups (n=774, 90.2%). Baseline clinical characteristics indicated that illiterate men were older at biopsy (p<0.001) and had higher tPSA (p=0.001) than men with incomplete or complete primary school and those with high school or college level education. There were no differences across educational groups with respect to distance from care site to BCH (p=0.43), year of biopsy (p=0.08), having an abnormal DRE (p=0.42), or family history of any cancer (p=0.07), especially PC (p=0.07). Men with high school or college level education were more likely to live closer to BCH, were younger, had the lowest PSA at biopsy, and higher percentage of the population had an abnormal DRE and family history of cancer (Table 6).

4.2.2. Risk of Non-Compliance

Our primary analysis, evaluating the risk of non-compliance, was performed in the subset of men who were recommended to biopsy at BCH (n=1,561). On crude analysis, non-compliance was significantly associated with increased distance from screening site to BCH relative to traveling distance less than 250km for care (250-500km: OR: 2.00, 95% CI: 1.40 – 2.85, 500-1000km: OR: 5.88, 95% CI: 4.07 – 8.51, $\geq$1000 km: OR: 15.98, 95% CI: 11.41 – 22.38, $p<0.001$, Table 5a). In our second crude analysis, increased educational attainment, relative to being illiterate, had an inverse association with non-compliance (incomplete primary: OR: 0.53, 95% CI: 0.42 – 0.68, complete primary: OR: 0.33, 95% CI: 0.19 – 0.58, $p<0.001$, high school + college: OR: 0.87, 95% CI: 0.48 – 1.56, $p=0.64$, Table 5b).

The risk of non-compliance by educational status was little changed after multivariable adjustment with age and biopsy year for education (Table 5b). The adjusted model, which included the interaction term for distance and education and was adjusted for both education and distance, indicated that there was no association between risk of non-compliance and the interaction of distance and education (Table 5c). Finally, the association between increased distance and non-compliance was little attenuated by multivariable adjustment with age and biopsy year with respect to the crude association (Table 5d).

4.2.3 Biopsy Outcomes

Of the 850 men who presented to BCH for a biopsy, 320 (37.7%) had cancer. Of the men with a positive biopsy, 65% had low-to-intermediate risk cancer as indicated by their Gleason score (Gleason 2 – 6), which was confirmed by pathological clinical staging (74.5% of cancers were Stage 1). The median number of cores taken at biopsy was 12 (IQR: 10 – 14) with the median number of cores that were positive of the total was 3 (IQR: 2 – 5). Measures of prostate volume (median: 33 cm^3, IQR: 25 – 46) were taken as well as a repeat tPSA for confirmation (median: 7 ng/mL, IQR: 4 – 16, Table 7) for all men.

4.2.4. The Association Between Education, Distance and Cancer on Initial Biopsy

The association between education and distance and having cancer on initial biopsy was performed using the subset of men who actually had a biopsy. On crude analysis, there was no association between distance from screening site to BCH (relative to $\leq$ 250km, Table 8a) and increased education (Table 8b) with having cancer on biopsy. Adjustment for age and the interaction term for education and distance in the refined model (Table 8c) did little to change the association between education, distance and cancer risk. Similar findings were observed in the final multivariable model upon removal of this interaction term (Table 8d).

4.2.5. Adjusted Associations Between Education, Distance and Cancer Grade on Initial Biopsy

The association between education and distance and cancer grade on initial biopsy was performed on the subset of men who had a positive biopsy. On crude analysis, relative to no cancer, there was no association between increased distance and low-grade cancer. For high-grade cancer, there was no association between the group of men who traveled 500-1000km (p=0.96) or those who traveled ≥1000km (p=0.15), however there was a significant association with men who traveled 250-500km relative to ≤250km (RRR: 2.44, 95% CI: 1.03 – 5.79, p=0.04, Table 9a). Education, categorized as a dichotomous variable, on crude analysis showed no association with both low and high-grade cancer relative to no cancer (Table 9b). The association between education and cancer grade changed little when adjusting for age, biopsy year, the interaction between distance and education, and total number of cores taken (Table 9c). Final adjustments to achieve our final multivariable model without the interaction term showed the same trend of no association between our exposures and our outcome (Table 9d).

4.3. Discussion

Population-level data surrounding PC incidence, mortality and incidence are limited in most Latin America countries, and Brazil in particular. While estimated Brazilian PC

incidence rate increases could be due to the increased use of widespread PSA testing (79.3 per 100,000 in 2002 and rising)[91], these numbers may be an underestimation of true incidence rates as they are likely non-inclusive of men living in rural areas with limited access to screening and health education about the disease.

In this study among men from a large-scale Brazilian screening cohort, we found that increased distance to care facility was significantly associated with increased risk of non-compliance to biopsy recommendations (2 – 16 times more likely), while lower education was significantly associated with a decreased risk of non-compliance. Though in this cohort the risk of high-grade cancer was low – 75% of detected cancers were classified as stage one - as predictors of cancer, there was no increased risk of having cancer on initial biopsy based on distance or education. In this case, stage distribution and the lack of association with education and distance could be a reflection of the substantial non-compliance rates. The men that were least compliant were those at greater distance from the hospital, with lesser access to health care, therefore, it is possible that the men with more advanced disease were less likely to present for biopsy and have their cancer confirmed.

With respect to cancer aggressiveness, there was no association between distance and low-grade cancer or education and low or high-grade cancer. However, there was an

association with high-grade cancer in the subset of men who traveled a moderate distance to receive care. Despite these negative results, the risk of high-grade cancer in this cohort was low which may have impacted our results.

Education, a marker of socioeconomic status, is widely used in public health studies as it is an easy to define metric, generalizable across multiple populations and is easy to collect. Furthermore, education can be used as an indicator of health literacy, knowledge of healthy lifestyle choices, and more informed health-seeking behaviors. Aside from academic achievement, the term education can also mean education about health. Lower education is correlated with adverse health outcomes due to limited comprehension of health concepts, exposure, and advice. These men may simply not understand the information imparted to them. The overall educational level of men in this cohort was unevenly distributed with the majority of men having low educational achievement. This suggests that the majority of men in our cohort were older as older generations are less likely to benefit from educational outreach, have health insurance, and come into contact with the health system. Thus we expected to see a correlation between noncompliance to biopsy recommendation and lower educational status based on the lack of ability to comprehend the importance of attending follow-up visits. Our findings were inconsistent with this observation.

Additionally, studies have shown that education is a marker for socioeconomic status[92] and that people in rural areas are more likely to have less access to education.[93] A study by Albano et al examined the effects of education and race on general cancer mortality in the US.[94] Their cohort of approximately 120 million people from the National Center for Health Statistics database examined mortality rates from multiple cancer types (including PC) using education level as the sole socioeconomic predictor. They found that among men with fewer than twelve complete years of education, the death rate from PC was almost double that of their higher education counterparts. A study by Reyes-Ortiz, which examined the effects of education and literacy levels among older Latin American adults are consistent with this finding.[90] An additional study based out of Sao Paolo, Brazil, which examined social inequalities among the elderly, indicated that elderly individuals with higher educational achievements had an overall lower prevalence of non-communicable diseases and PC risk factors.[95] Our hypothesis, that less education is associated with higher PC incidence and aggressiveness has been contradicted by our findings. This contradictory finding could be due to low numbers of enrollment of men with high educational achievement who live in these rural areas or exclusion based on previous screening attempts at different care centers.

Geographic distance to care is a barrier restricting health system access around the world, however data evaluating the association of geographic distance to care and cancer

outcomes are limited. According to the literature, this is the first study conducted in PC. A study by Seal et al in colorectal cancer showed that men who live further away from care centers are less incentivized to participate in clinical trials, follow-up exams and attend routine provider visits for preventive care.[96] An additional study by Katarai in 2011 found consistent findings.[97] However, these studies compared distances of 25 or 50 miles, as opposed to our study where the distances are greater and the potential challenges to get to BCH from the screen site are increased. As the majority of the men in our cohort lived within 500km of BCH, we expected to see an increased risk of noncompliance to biopsy recommendations, which we did. Our findings were consistent with their results. Regarding cancer outcomes, we expected to see a correlation between increased distance from care center and more aggressive tumors. Our findings, however, did not find a relationship consistent with this hypothesis. The inclusion of the interaction term, for example, suggesting that lower education and longer distance would be correlated with increased risk of noncompliance, cancer on biopsy and more aggressive cancer showed no relationship. These results could be due to low numbers of high-grade cancers found in this cohort, low numbers of men with high educational attainment, few numbers of men who lived further away, nonparametric distribution of distance data, or a combination of the above.

Our study has several limitations most important of which is the fact that these data were not collected with research intent. Therefore, the potential for information bias is high. As a collective part of a cancer outreach screening program[64], these men gave their data to health care providers in order to receive free recommendations on their cancer risk. This could also be a source of concern ethically as these men did not consent for their data to be used for research. Additionally, if a screening program is implemented, it's important to have reasonable systems in place to follow up on abnormal findings. Asking men to travel many hundreds of miles for follow-up is ethically questionable, especially for a test like PSA that has many limitations and problems. Additional studies are needed to determine if the risk of PC and PC aggressiveness stratified by socioeconomic status holds with more reasonable follow-up guidelines for the men who are recommended to biopsy but live very far away.

Despite these limitations, there are several key strengths of this study. Given the high level of illiteracy, investigators contacted men whose biopsy indications were suspicious of PC by mail or by phone. By including a phone call as a method of notification, it insures that the men received the information and were able to understand it. If notifications were only by mail, this could be a major explanatory variable for the low follow-up rates in the illiterate men. Secondly, contamination issues commonly seen in large-scale screening studies were minimized as we restricted analysis only to men who

are having a first screen and/or biopsy. This eliminates the biases introduced by repeat biopsies and repeat screen attempts. Thirdly, there were standardized methods of data collection before and during screening for each enrolled subject. Of the men analyzed, all had complete pre-clinical and demographic data recorded in medical records, which were included in analysis. Furthermore, the availability of complete data minimizes the effect and/or potential for recall bias with respect to cancer outcomes and cancer aggressiveness. As all pre-biopsy screens were done offsite, all sample collections and DRE exams were administered by the same personnel, therefore ensuring uniformity in classification of cancer status, and that all blood samples that were measured for PSA were treated the same way. Regarding post-screen biopsies, there was limited variability in the number of cores taken per patient recommended to biopsy (median: 12, IQR: 10-14), which is consistent with worldwide recommendations to take twelve cores per prostate to optimize detection of cancer.[98] It is clear that despite these strengths, this negative study is by no means conclusive or representative of the true relationship among education, distance to care, noncompliance and cancer outcomes in an underprivileged, developing world setting. Additional studies are needed to fully test the relationship of these health disparity indicators with outcomes to fully understand the link between socioeconomics and cancer risk.

4.4. Conclusion

In a Brazilian cohort of men undergoing PC screening, we found that educational attainment, a social marker for socioeconomic status, was not associated with an increased risk of overall PC on initial prostate biopsy even after adjusting for key clinical characteristics. Additionally, we found that distance from screening site to follow-up care facility, though a risk factor for non-compliance to biopsy recommendations, was also not positively associated with risk of PC or cancer grade on initial biopsy. This suggests that when all else is equal, only distance is a factor when assessing compliance to PC biopsy recommendations, and that additional research into risk factors of cancer and cancer grade in underprivileged regions on biopsy are needed.

5. Perspectives

The global burden of cancer is increasing worldwide. Increasing life expectancies as well as the number of countries that are in economic transition from lower-middle income to middle income has resulted in a marked increase in cancer cases and cancer mortality. Thus, cancer has emerged as a forefront global public health priority[99].

This thesis provides evidence that socioeconomic health disparities influence PC detection on initial biopsy. While other studies have evaluated these indices in other cancers and after PC treatment, these studies are evaluating them at the beginning of diagnostic timeline. By choosing this time-point, we sought to understand where potential interventions could be most useful in preventing PC and minimizing potential risk.

Our studies, which evaluated the role of race, educational status and distance from primary screen site to follow-up care facility with cancer status and aggressiveness on initial biopsy, provided encouraging results that will not only require additional studies, but also shed light on the multifaceted nature of PC. Nonetheless, it is important to address the broad implications of these findings, limitations and suggest future directions for further investigation.

Our US-based study on race and PC risk and aggressiveness on initial biopsy found that black race was significantly associated with an overall increased risk of having cancer on initial biopsy, especially low-grade cancer. While a strength of this study was that it was performed in an equal-access hospital with intention of minimizing access to care and socioeconomic confounding[100], our data suggest that perhaps the mechanism behind this phenomenon is biological. As such, what needs to be understood is what it is about race that makes black men at higher risk when all external things are essentially equal.

Race, in the US, is both a social and a biological construct that encompasses many different facets. Socially, race could describe one's diet, lifestyle, anthropologic and cultural choices, whereas biologically, race is defined by ancestral informative markers or single nucleotide polymorphisms associated with skin pigmentation.[101] Our data was self-report and collected retrospectively, therefore, we evaluated race as a social construct. While this can be viewed as a strength of the study – that men were allowed to classify themselves relative to how they best identified – what remains to be seen is if these men were classified based on their biological race, would the same patterns of risk be seen.

Because we evaluated race as a social and not biological construct with respect to PC risk, we potentially introduced bias into our models and therefore our results. The potential for misclassification as a result of data being abstracted from patient medical

records is high. We controlled for this by only using men who had complete data available for the variables we chose to include. Additionally, to control for potential confounding due to PSA, DRE and prostate volume, we evaluated models that included and excluded these variables and elected to remove them from our analysis. The potential for both selection and information bias also existed within our analyses. As aforementioned, the number of biopsy cores taken per patient varies and has increased over time from the early 1990s until about 2001. As such, by taking more biopsy cores, a provider has an increased likelihood of detecting cancer on initial biopsy relative to before when fewer cores were taken. To eliminate the potential for selection bias, we elected to evaluate models that controlled for biopsy year over the total number of cores taken as with increasing biopsy year increased number of cores were taken up to 2001. Finally, the potential for information bias exists in retrospective cohorts, which may influence the power of our results. One potential source for information bias lies in the fact that we are evaluating data from a VA patient population. One study suggested that VA populations are not representative of the general North Carolina population[102, 103] that may seek treatment at a university-sponsored hospital[104] nor of the general US population as they have lower rates of cancer mortality relative to the whole.[105] Furthermore, patients at VA hospitals are typically different than people in the generalized population. These men and women have health care access, have a relatively standardized level of education, have access to preventive care measures, and have encountered the healthcare

system.[106] VA patients also have, in general, poorer health status and lower socioeconomic status than the general population.[107] The same cannot be said for every American. Thus, while the findings of our DVAMC study suggest a role in race and PC risk and aggressiveness, future studies that can deconstruct and evaluate the social components of "race" and evaluate them independently along with PC risk and aggressiveness are needed.

Our Brazilian-based early PC detection screening program found no association between educational status and distance with PC risk and aggressiveness, but did find an increased association between risk of non-compliance to biopsy recommendations with distance to follow-up care center. While it is known that people in developing countries have less access to health care relative to their developed country, distance and education contribute to this phenomenon by way of socioeconomic status and income. It can easily be argued that those in poverty are undereducated and live in rural areas with limited health services access. The gap between the rich and poor is further exacerbated by financial barriers – i.e. not having the money to travel to receive health care, or not having the luxury of taking the time away from work to go to receive health care – as well as informational ones – for example, not understanding the importance of screening, medical literature, or knowing what to ask providers when contact is made. It is of most importance, to understand how disease affects these rural populations such that when

healthcare is needed they have access to it, decreasing the risk of illness caused by poverty.[48] Specific to PC, studies have linked low socioeconomic status with increased risk of dying from PC[108, 109] and low educational status with risk of not using early detection screening for PC in Latin American populations.[90] Knowing this, it seemed appropriate to evaluate the association between risk of noncompliance to biopsy recommendation, PC risk and PC aggressiveness with distance and education.

Our initial hypothesis that increased distance and lower education would be associated with increased risk of non-compliance and increased risk of overall PC was based on the premise that distance and education could be used as indicators of socioeconomic status. Like education, distance is a complex variable with multiple implications in public health research. Increased distance can also imply restricted access. For example, measures of distance can encompass geographical distance (km) or physical distance (terrain). Given that our hypothesis was based on using geographical distance to care without factoring in additional burdens such as finding transportation[110], the challenge of lost wages, and physical barriers to screening, finding a variable that better encompasses the essence of what is actually faced by patients is needed in order to determine whether or not distance really matters in the ability to predict disease risk and minimize risk of non-compliance. While some literature has shown that the further away a person resides from a provider, the less likely they are to come in for routine, follow-up, and screening exams,[111] others

have shown distance to not be a barrier to receiving care.[112] Despite conflicting findings, what is left to be determined is whether these measures of distance capture the essence of the same construct used to predict adherence and risk. Unfortunately, distance is not just a barrier for patients to overcome. Distance challenges are characterized by fewer number of care centers in rural areas, fewer physicians with heavier patient loads, and fewer incentives for physicians to practice in rural areas due to lower compensation.[113] One strength of our study is the fact that so many distances (range from 0 – 1500+ km) are included in our dataset that we have the capability to examine at what point distance from care center no longer matters with respect to compliance, PC risk and PC aggressiveness in an environment where the number of care facilities available for initial screening is irrelevant.

With respect to education, we hypothesized that lower educational attainment would be correlated with increased risk of non-compliance, overall PC, and PC aggressiveness and found no associations. The literature has shown that low education is associated with higher disease mortality[114] in a study of US cancer patients[115] but what is unclear is the role education plays in adherence or inhibits health related decisions. For the purposes of our study, we used education as a marker of socioeconomic status – a compounded variable that encompasses a multitude of markers depending on context. More specifically, low education could include the level of formal education obtained – which

is related to potential future earnings and income, low knowledge about health and disease, low health literacy, and lower ability to comprehend health communications with providers. Unfortunately, given that there is no defined metric as to what educational status means and what it measures, this leaves the door open for potential misclassification and interpretation biases in large datasets wherein education may not capture what investigators hope it will.

As such, despite the multiple meanings and potential applications of our exposure variables, our Brazilian study did highlight several areas where additional study is needed. For example, with respect to education, our study had a small sample size for patients in higher echelons of educational attainment. Thus, additional studies more inclusive of more people with higher levels of educational achievement is needed. Furthermore, this cohort was comprised of men with a relatively low cancer detection rate, which may have impacted our ability to determine differences in predictability between education and distance and overall risk and aggressiveness. While the findings of this study are generally negative, additional studies that further explore how education, like race, is a multifaceted variable and identify the components thereof, and how to better use distance combined with income to terse out the relationship between health services access and compliance, are needed.

Overall, the independent studies presented in this thesis have shown that health disparities do play a role in predicting cancer risk and aggressiveness though the mechanism through which they independently act still needs to be explored. Though we did not study the relationship between these indices and survivorship, recurrence, or factors pertaining to disease onset, the biological mechanism through which race mediates tumor growth – be it genetics, epigenetics, or environment – and the ways in which education and distance modify the risk of compliance leave the door open for future studies. Additionally, these studies set the stage for identifying points at which interventions aimed at lowering risk, promoting screening, and increasing healthy preventive behaviors can curb the risk and aggressiveness of PC in elderly men at above average disease risk.

Appendix A: Figures

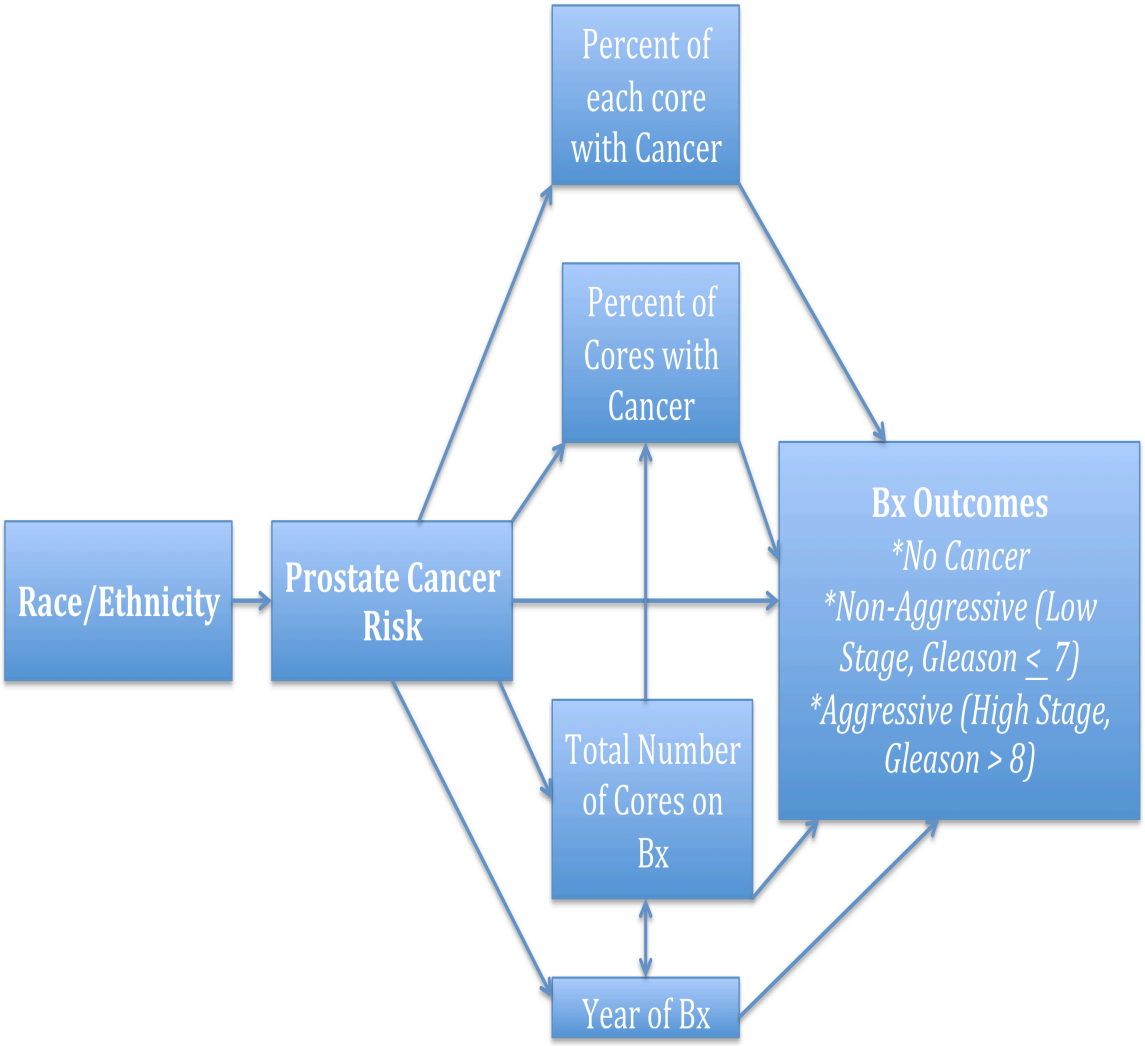

Figure 1 – Predictors of PC Cancer Grade on Initial Biopsy (Durham VA Biopsy Study)

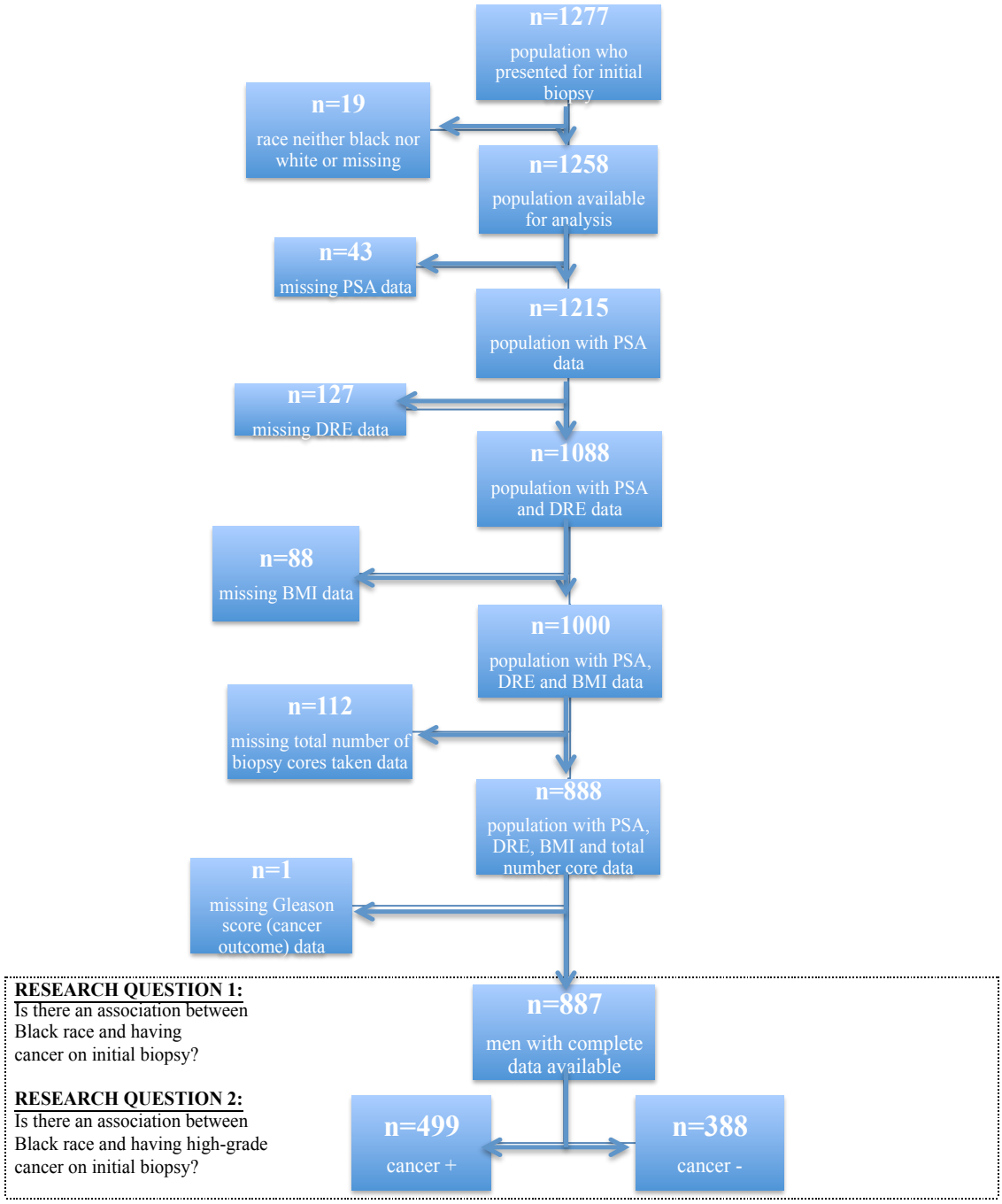

Figure 2 - Flowchart Describing PC Screening Cohort (Durham VA Biopsy Study)

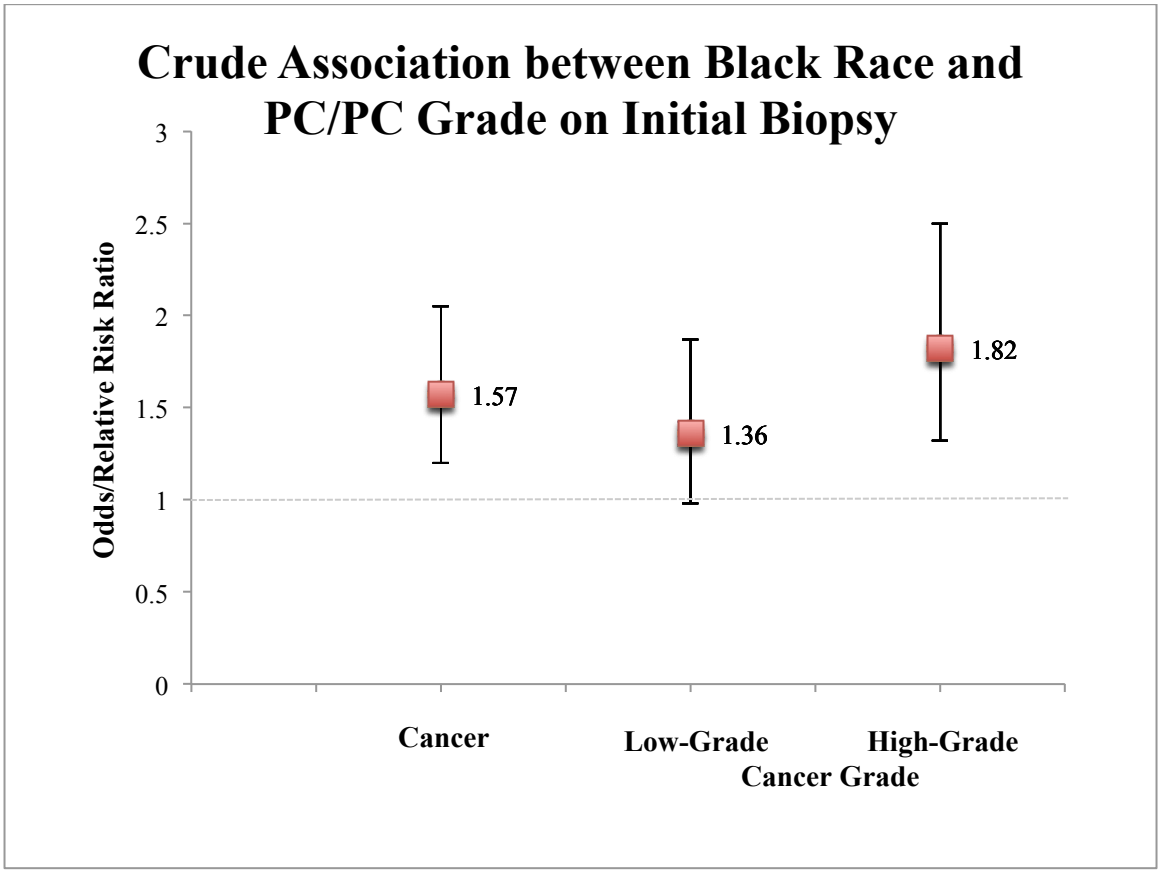

Figure 3 – Crude Association between Black Race and PC/PC Grade on initial biopsy (Durham VA Biopsy Study)

Statistical Analysis: Logistic Regression for Cancer on Biopsy (OR); Multinomial Logistic Regression for Cancer Grade on Biopsy (RRR)

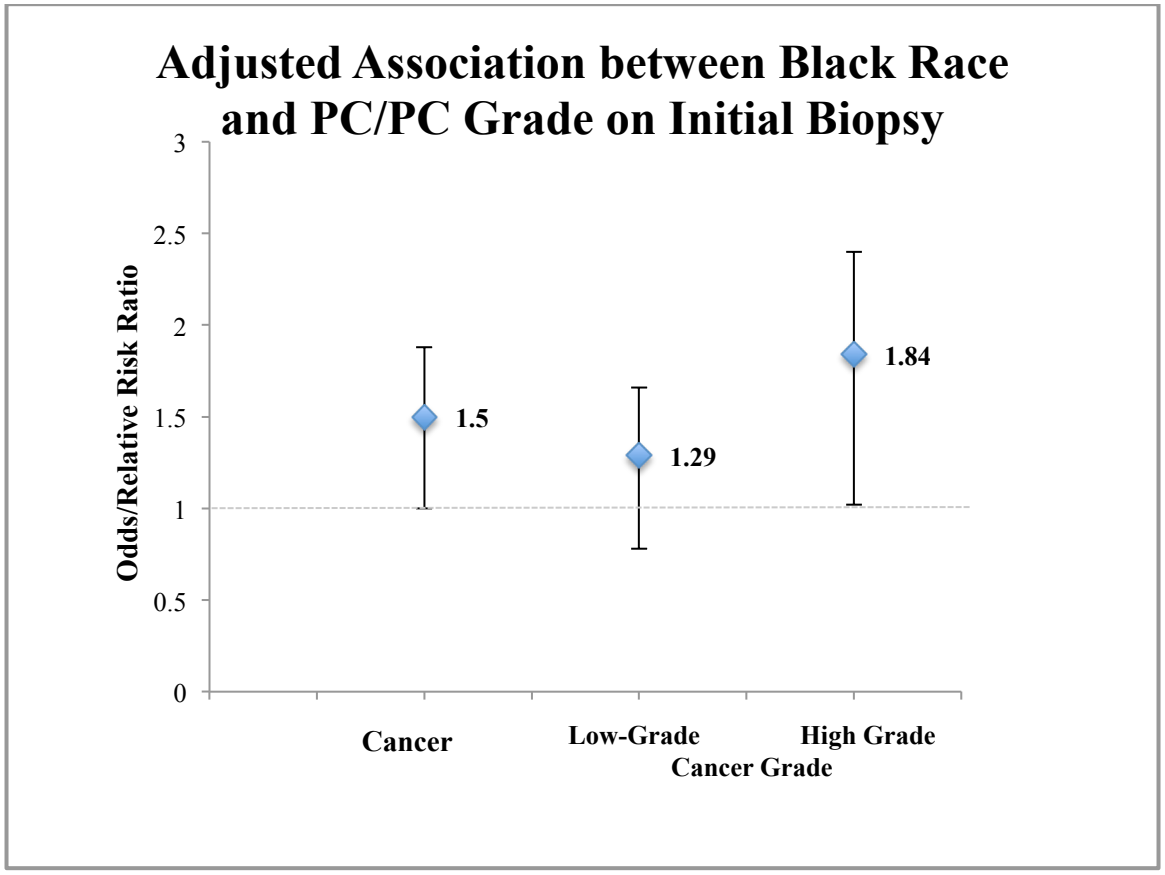

Figure 4 – Adjusted Association between Black race and PC/PC Grade on initial biopsy (Durham VA Biopsy Study)

Statistical Analysis: Logistic Regression for Cancer on Biopsy (OR); Multinomial Logistic Regression for Cancer Grade on Biopsy (RRR)

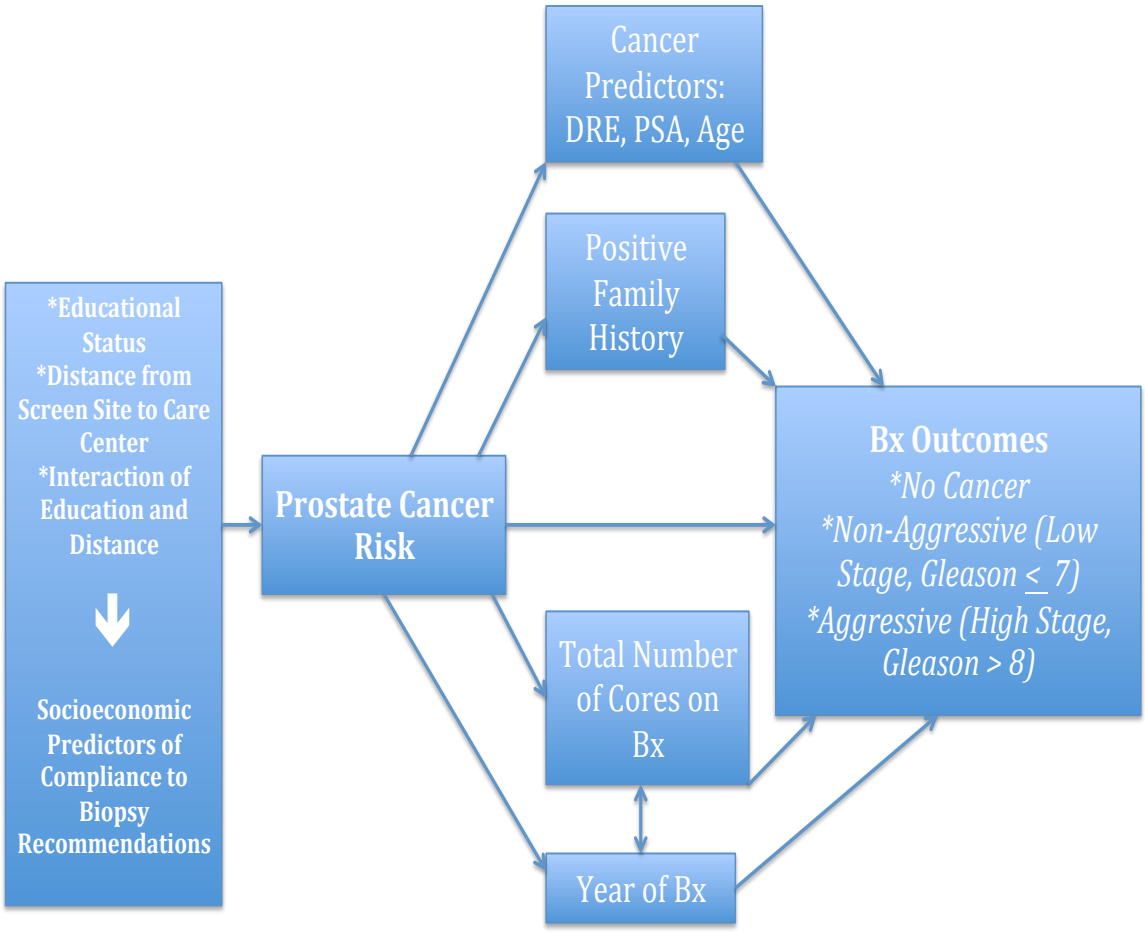

Figure 5 – Predictors of PC Grade on Initial Biopsy (Barretos Cancer Hospital Screening Study

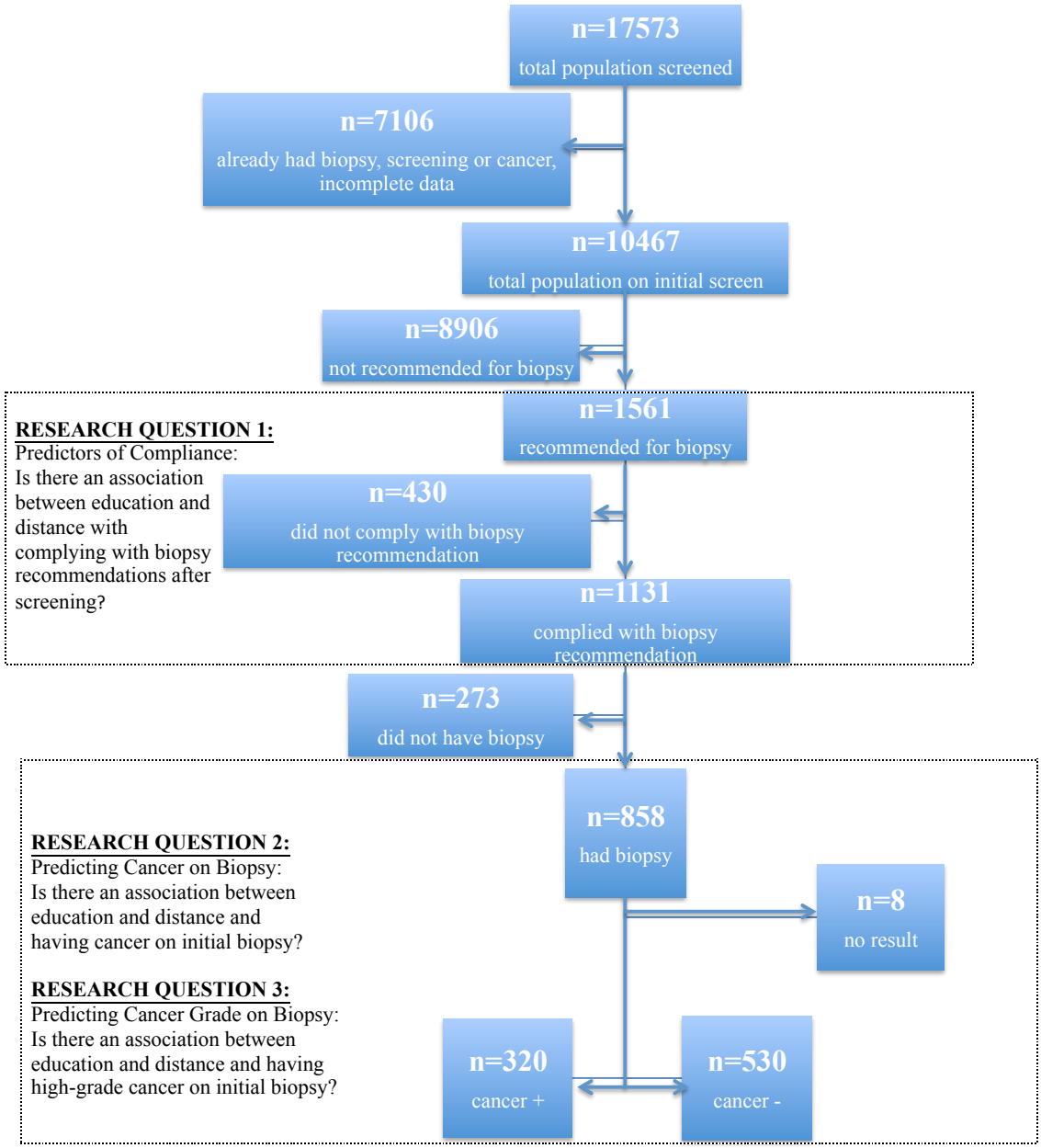

Figure 6 – Flowchart Describing PC Screening Cohort (Barretos Cancer Hospital Study)

Appendix B: Tables

Table 1 – Clinical characteristics for men undergoing an initial prostate biopsy at the DVAMC, 2001 – 2009 with complete data for all variables (n=887).

Clinical Characteristics at Baseline	Black N = 431	White N = 456	*P**
	Median (IQR)	**Median (IQR)**	
Year of Biopsy	**2005** (2002 – 2006)	**2004** (2002 – 2006)	0.290
Total Number of Cores Taken	**11** (8 – 12)	**11** (8 – 12)	0.842
Age at Biopsy (years)	**61** (57 – 68)	**65** (60 – 70)	<0.001
PSA (ng/mL)	**6.6** (4.7 – 12.1)	**5.8** (4.4 – 8.4)	0.001
	No. (%)	**No. (%)**	***P*+**
BMI (kg/m^2)			0.321
< 25 kg/m^2	**110** (25.5)	**100** (21.9)	
25 - 29.99 kg/m^2	**160** (37.1)	**188** (41.2)	
30 – 34.99 kg/m^2	**114** (26.5)	**109** (23.9)	
≥ 35 kg/m^2	**47** (10.9)	**59** (12.9)	
Abnormal DRE	**109** (25.3)	**141** (30.9)	0.062

Statistical analyses: * = rank-sum test; + = chi-squared test
BMI = body mass index; DRE = digital rectal exam; DVAMC = Durham Veteran Affairs Medical Center; IQR = Interquartile Range; P = p-value; PSA = prostate specific antigen

Table 2 – Biopsy outcomes for men on initial prostate biopsy at the DVAMC, 2001 – 2009 with complete data for all variables (n=887).

Biopsy Outcomes	Black N = 431	White N = 456	*P**
	No. (%)	**No.** (%)	
Biopsy outcome			0.001
No cancer	**164** (38.1)	**224** (49.1)	
Any cancer	**267** (61.9)	**232** (50.9)	
Low-Grade (< 7)	**122** (28.3)	**123** (27.0)	
High-Grade (≥ 7)	**145** (33.6)	**109** (23.9)	
	Median (IQR)	**Median (IQR)**	P^+
Total number of positive cores among men with cancer, IQR	**4** (2 – 6)	**3** (1 – 6)	0.084

Statistical Analyses: * = Rank-sum test for comparison of three outcome categories (no cancer, low-grade, high-grade), $^+$ = Chi-Squared test

DVAMC = Durham Veteran Affairs Medical Center; IQR = Interquartile Range; P = p-value for comparison of black to white men.

Table 3 – Black race as an independent predictor of cancer and cancer grade on initial biopsy at the DVAMC, 2001 – 2009 with complete data for all variables (n=887).

Cancer on Biopsy			
Type of Analysis	**OR**	**95% CI**	***P***
Crude	1.57	1.20 – 2.05	<0.001
Adjusted Multivariable	1.50	1.12 – 2.00	0.006
Cancer Grade on Biopsy			
	RRR	**95% CI**	***P***
Crude Multinomial, Relative to No Cancer			
Low-Grade (< 7)	1.36	0.98 – 1.87	0.064
High-Grade (≥ 7)	1.82	1.32 – 2.50	<0.001
Adjusted Multinomial, Relative to No Cancer			
Low-Grade (< 7)	1.29	0.92 – 1.80	0.139
High-Grade (≥ 7)	1.84	1.28 – 2.66	0.001

Statistical Analysis: Logistic Regression for Cancer on Biopsy; Multinomial Logistic Regression for Cancer Grade on Biopsy

OR = odds ratio for black race vs. white race; RRR = relative risk ratio for no cancer vs. low-grade vs. high-grade; CI = confidence interval; P = p-value

Models adjusted for age, log-PSA, BMI, DRE and total number of cores taken

Table 4 – Descriptive Baseline Characteristics of Men Undergoing Initial PC Screening by Brazilian Mobile Medical Units stratified by compliance to biopsy recommendation, 2004-2007.

	Men undergoing initial PSA screening who were recommended for biopsy and complied with the biopsy recommendation	Men undergoing initial PSA screening who were recommended for biopsy and did not comply with the biopsy recommendation	P-Values for men who complied vs. did not comply amongst those recommended to biopsy
Predictors of Compliance	**No. (%)**		**P[+]**
	N = 1,131 (72.5)	**N = 430** (27.5)	
Distance from Barretos (km)			<0.001
0 – 249.99 km	**620** (54.8)	**75** (17.4)	
250 – 499.99 km	**289** (25.6)	**70** (16.3)	
500 – 999.99 km	**118** (10.4)	**84** (19.5)	
≥ 1000 km	**104** (9.2)	**201** (46.7)	
Educational Level Attained			<0.001
Illiterate	**279** (24.7)	**165** (38.4)	
Incomplete Primary	**729** (64.5)	**229** (53.3)	
Complete Primary	**86** (7.6)	**17** (4.0)	
High School	**30** (2.7)	**15** (3.5)	
College	**7** (0.6)	**4** (0.9)	
Year of Screening			<0.001
2004	**230** (20.3)	**82** (19.1)	
2005	**355** (31.4)	**80** (18.6)	
2006	**333** (29.4)	**102** (23.7)	
2007	**213** (18.8)	**166** (38.6)	
Positive Family History			
PC	**56** (5.0)	**14** (3.3)	0.15
Any Cancer	**122** (10.8)	**33** (7.7)	0.07
DRE Suspicious of PC	**378** (33.4)	**84** (19.5)	<0.001
	Median (IQR)		**P[*]**
Age (years)	**66** (59 – 72)	**68** (62 – 74)	<0.001
Total PSA (ng/mL)	**4.17** (2.58 – 7.14)	**4.90** (3.45 – 7.72)	<0.001

Statistical Analyses: * = rank-sum test; [+] = chi-squared test
DRE = digital rectal exam; IQR = interquartile range; P = p-value; PC = prostate cancer; PSA = serum prostate specific antigen (ng/mL

Table 5 – Association between Education, Distance & Risk of Non-Compliance (n=1561)

Table 5a – Is there an association between distance and non-compliance?

Model	Categories	OR	95% CI	P-Value[#]
Distance (Relative to 0 – 249.99 km)				
Crude	250 – 499.99 km	2.00	1.40 – 2.85	<0.001
	500 – 999.99 km	5.88	4.07 – 8.51	
	≥ 1000 km	15.98	11.41 – 22.38	
Adjusted for Age Unrestricted	**250 – 499.99 km**	**1.95**	**1.37 – 2.79**	**<0.001**
	500 – 999.99 km	**5.97**	**4.12 – 8.66**	
	≥ 1000 km	**15.86**	**11.29 – 22.27**	
Adjusted for tPSA	250 – 499.99 km	1.89	1.32 – 2.70	<0.001
	500 – 999.99 km	5.53	3.80 – 8.06	
	≥ 1000 km	15.18	10.70 – 21.53	
Adjusted for Biopsy Year	**250 – 499.99 km**	**1.89**	**1.32 – 2.70**	**<0.001**
	500 – 999.99 km	**5.53**	**3.80 – 8.05**	
	≥ 1000 km	**14.88**	**10.57 – 20.95**	
Adjusted for Abnormal DRE	250 – 499.99 km	1.90	1.32 – 2.73	<0.001
	500 – 999.99 km	5.52	3.77 – 8.08	
	≥ 1000 km	15.16	10.64 – 21.58	
Adjusted for Family History of Any Cancer	250 – 499.99 km	1.88	1.32 – 2.70	<0.001
	500 – 999.99 km	5.53	3.80 – 8.06	
	≥ 1000 km	15.15	10.72 – 21.39	
Adjusted for Family History of PC	250 – 499.99 km	1.89	1.32 – 2.70	<0.001
	500 – 999.99 km	5.53	3.80 – 8.06	
	≥ 1000 km	15.15	10.72 – 21.40	

Statistical Analyses: Logistic Regression; # = likelihood ratio test
tPSA = logarithmically-transformed; CI = confidence interval; km = kilometers; PC = prostate cancer

Table 5 – Association between Education, Distance & Risk of Non-Compliance (n=1561) (continued)

Table 5b – Is there an association between educational achievement and non-compliance?

Model	Categories	OR	95% CI	P-Value
Education (Relative to Illiterate)				
Crude	Incomplete Primary	0.53	0.42 – 0.68	<0.001
	Complete Primary	0.33	0.19 – 0.58	
	High School + College	0.87	0.48 – 1.56	
Adjusted for Age Unrestricted	**Incomplete Primary**	**0.60**	**0.47 – 0.77**	**<0.001**
	Complete Primary	**0.39**	**0.22 – 0.68**	
	High School + College	**1.11**	**0.61 – 2.03**	
Adjusted for tPSA	Incomplete Primary	0.59	0.46 – 0.77	<0.001
	Complete Primary	0.41	0.23 – 0.73	
	High School + College	1.15	0.62 – 2.13	
Adjusted for Biopsy Year	**Incomplete Primary**	**0.58**	**0.45 – 0.75**	**<0.001**
	Complete Primary	**0.40**	**0.23 – 0.71**	
	High School + College	**1.13**	**0.61 – 2.07**	
Adjusted for Abnormal DRE	Incomplete Primary	0.59	0.46 – 0.72	<0.001
	Complete Primary	0.43	0.24 – 0.76	
	High School + College	1.21	0.65 – 2.25	
Adjusted for Family History of Any Cancer	Incomplete Primary	0.59	0.46 – 0.76	<0.001
	Complete Primary	0.41	0.23 – 0.72	
	High School + College	1.15	0.62 – 2.12	
Adjusted for Family History of PC	Incomplete Primary	0.59	0.46 – 0.76	<0.001
	Complete Primary	0.41	0.23 – 0.72	
	High School + College	1.15	0.62 – 2.12	

Statistical Analyses: Logistic Regression
tPSA = logarithmically-transformed; CI = confidence interval; PC = prostate cancer

Table 5 – Association between Education, Distance & Risk of Non-Compliance (n=1561) (continued)

Table 5c – Refined Multivariable Model of the Association between Distance and Education and non-compliance.

Refined Model with Interaction Term				
Variable	**Categories**	**OR**	**95% CI**	**P-Value**
Education (relative to Illiterate)	Incomplete Primary	0.62	0.43 – 0.88	0.003#
	Complete Primary	0.49	0.24 – 1.01	
	High School + College	1.24	0.49 – 3.18	
Distance (relative to 0 – 249.99 km)	250 – 499.99 km	1.86	1.29 – 2.67	<0.001
	500 – 999.99 km	5.29	3.53 – 7.94	
	≥ 1000 km	14.04	8.56 – 23.03	
Age		1.03	1.01 – 1.04	<0.001
Biopsy Year		1.21	1.07 – 1.36	0.003
Distance x Education				0.84

Statistical Analyses: Logistic Regression, # = Likelihood Ratio Test
Multivariable Analysis adjusted for Age and Biopsy Year; tPSA = logarithmically-transformed
CI = confidence interval; km = kilometers; PC = prostate cancer

Table 5 – Association between Education, Distance & Risk of Non-Compliance (n=1561) (continued)

Table 5d – Multivariable Analyses of Distance and Educational Achievement Non-Compliance

Variable	Categories	OR	95% CI	P-Value[#]
Education (relative to Illiterate)	Incomplete Primary	0.63	0.47 – 0.84	0.002
	Complete Primary	0.51	0.27 – 0.94	
	High School + College	1.32	0.65 – 2.67	
Distance (relative to 0 – 249.99 km)	250 – 499.99 km	1.87	1.30 – 2.68	<0.001
	500 – 999.99 km	5.37	3.68 – 7.84	
	≥ 1000 km	14.60	10.34 – 20.60	

Statistical Analyses: Logistic Regression, # = Likelihood Ratio Test
Multivariable Analysis adjusted for Age and Biopsy Year; tPSA = logarithmically-transformed
CI = confidence interval; km = kilometers; PC = prostate cancer

Table 6 – Descriptive Baseline Clinical Characteristics of Men who Underwent Initial Biopsy stratified by Educational Status at Barretos Cancer Hospital, Barretos, SP, Brazil (n=858)

Baseline Clinical Characteristics	Educational Status				
	Illiterate	Incomplete Primary School	Complete Primary School	High School & College	
	N = 223 (26.0)	N = 551 (64.2)	N = 60 (7.0)	N = 24 (2.8)	P*
	Median (IQR)				
Age (years)	**69** (64 – 76)	**65** (59 – 71)	**64** (56 – 72)	**58** (53 – 65)	<0.001
Total PSA (ng/mL)	**6.04** (3.65 – 11.87)	**4.47** (2.94 – 7.43)	**4.73** (2.57 – 9.08)	**4.16** (2.75 – 7.68)	0.001
	No (%)				P+
Distance from Barretos (km)	**103** (46.2)	**301** (54.6)	**33** (55.0)	**16** (66.7)	0.43
0 – 249.99 km	**67** (30.0)	**139** (25.2)	**18** (33.0)	**3** (12.5)	
250 – 499.99 km	**28** (12.6)	**55** (10.0)	**4** (6.7)	**3** (12.5)	
500 – 999.99 km	**25** (11.2)	**56** (10.2)	**5** (8.3)	**2** (8.3)	
> 1000 km					
Year of Screening					0.08
2004	**52** (23.3)	**111** (20.2)	**12** (20.0)	**5** (20.8)	
2005	**64** (28.7)	**161** (29.2)	**29** (48.3)	**7** (29.2)	
2006	**62** (27.8)	**174** (31.6)	**14** (23.3)	**10** (41.7)	
2007	**45** (20.2)	**105** (19.1)	**5** (8.3)	**2** (8.3)	
DRE Suspicious of PC	**47** (21.1)	**139** (25.2)	**13** (21.7)	**8** (33.3)	0.42
Positive Family History					
Any Cancer	**14** (6.3)	**60** (10.9)	**6** (10.0)	**5** (20.8)	0.07
PC	**4** (1.8)	**22** (4.0)	**5** (8.3)	**2** (8.3)	0.07

Statistical Tests: * = analysis of variance test (ANOVA); + = chi-squared test

Table 7 – Prostate Biopsy Outcomes among men undergoing initial biopsy after recommendation by Brasilian Mobile Medical Units following an abnormal screen, 2004-2007.

Biopsy Outcomes	No. (%)
Cancer Status on First Biopsy	
Positive	**320** (37.7)
Negative	**530** (62.4)
Cancer Details among men with Cancer and Complete Data, N = 318	
Gleason Score	
2 – 6	**207** (65.1)
7	**85** (26.7)
8 – 10	**26** (8.2)
Clinical Stage	
Stage I	**237** (74.5)
Stage II	**42** (13.2)
Stage III	**16** (5.0)
Stage IV	**23** (7.2)
Transrectal Ultrasound Findings	
Normal	**106** (33.3)
Hypoechoic Nodules	**211** (66.4)
Hyperechoic Nodules	**1** (0.3)
	Median (IQR)
Total Number of Positive Cores	**3** (2 – 5)
Total Number of Cores Taken	**12** (10 – 14)
Prostate Volume (cc)	**33** (25 – 46)
tPSA (ng/mL)	**7** (4 – 16)

Table 8 – The Association between Education and Distance and Cancer on Initial Biopsy of all men who had a biopsy (n=858)

Table 8a – Is there an association between distance and having cancer on initial biopsy?

Model	Categories	OR	95% CI	P-Value[#]
Distance (Relative to 0 – 249.99 km)				
Crude	**250 – 499.99 km**	**1.05**	**0.76 – 1.46**	**0.37**
	500 – 999.99 km	**0.87**	**0.54 – 1.40**	
	≥ 1000 km	**1.45**	**0.91 – 2.30**	
Adjusted for Age Unrestricted	250 – 499.99 km	1.05	0.75 – 1.46	0.34
	500 – 999.99 km	0.89	0.55 – 1.45	
	≥ 1000 km	1.50	0.94 – 2.38	
Adjusted for Total Number of Cores Taken	250 – 499.99 km	1.01	0.72 – 1.41	0.37
	500 – 999.99 km	0.84	0.52 – 1.36	
	≥ 1000 km	1.43	0.90 – 2.28	
Adjusted for Biopsy Year	250 – 499.99 km	1.01	0.72 – 1.41	0.37
	500 – 999.99 km	0.81	0.50 – 1.32	
	≥ 1000 km	1.40	0.87 – 2.24	
Adjusted for Family History of Any Cancer	250 – 499.99 km	0.99	0.71 – 1.39	0.32
	500 – 999.99 km	0.81	0.50 – 1.32	
	≥ 1000 km	1.43	0.89 – 2.30	
Adjusted for Family History of PC	250 – 499.99 km	0.99	0.71 – 1.39	0.33
	500 – 999.99 km	0.81	0.50 – 1.33	
	≥ 1000 km	1.43	0.89 – 2.30	

Statistical Analyses: Logistic Regression, # = Likelihood Ratio Test
CI = confidence interval; km = kilometers; PC = prostate cancer

Table 8 – The Association between Education and Distance and Cancer on Initial Biopsy of all men who had a biopsy (n=858) (continued)

Table 8b – Is there an association between educational achievement and having cancer on initial biopsy?

Model	Categories	OR	95% CI	P-Value[#]
Education (Relative to Illiterate)				
Crude	Incomplete Primary	1.03	0.75 – 1.42	0.57
	Complete Primary	0.89	0.49 – 1.62	
	High School + College	0.55	0.21 – 1.44	
Adjusted for Age Unrestricted	**Incomplete Primary**	**1.17**	**0.84 – 1.63**	**0.66**
	Complete Primary	**1.06**	**0.58 – 1.96**	
	High School + College	**0.78**	**0.29 – 2.07**	
Adjusted for Total Number of Cores Taken	Incomplete Primary	1.18	0.85 – 1.65	0.63
	Complete Primary	1.09	0.59 – 2.02	
	High School + College	0.76	0.28 – 2.04	
Adjusted for Biopsy Year	Incomplete Primary	1.17	0.84 – 1.63	0.69
	Complete Primary	1.13	0.61 – 2.09	
	High School + College	0.78	0.29 – 2.10	
Adjusted for Family History of Any Cancer	Incomplete Primary	1.16	0.83 – 1.62	0.68
	Complete Primary	1.12	0.61 – 2.07	
	High School + College	0.75	0.28 – 2.01	
Adjusted for Family History of PC	Incomplete Primary	1.16	0.83 – 1.62	0.68
	Complete Primary	1.12	0.60 – 2.06	
	High School + College	0.75	0.28 – 2.02	

Statistical Analyses: Logistic Regression; # =Likelihood Ratio Test
CI = confidence interval; PC = prostate cancer

Table 8 – The Association between Education and Distance and Cancer on Initial Biopsy of all men who had a biopsy (n=858) (continued)

Table 8c – Refined Multivariable Model of the Association between Distance and Education and having cancer on initial biopsy.

Refined Model with Interaction Term				
Variable	**Categories**	**OR**	**95% CI**	**P-Value**
Education (relative to Illiterate)	Incomplete Primary	1.24	0.85 – 1.81	0.62[#]
	Complete Primary	1.17	0.59 – 2.32	
	High School + College	0.92	0.30 – 2.86	
Distance (relative to 0 – 249.99 km)	250 – 499.99 km	1.08	0.76 – 1.52	0.39[#]
	500 – 999.99 km	0.95	0.56 – 1.60	
	$\geq$ 1000 km	1.72	0.85 – 3.49	
Age		1.04	1.02 – 1.05	<0.001
Distance x Education				0.60

Statistical Analyses: Logistic Regression, # = Likelihood Ratio Test
Multivariable Analysis adjusted for Age
CI = confidence interval; km = kilometers; PC = prostate cancer

Table 8 – The Association between Education and Distance and Cancer on Initial Biopsy of all men who had a biopsy (n=858) (continued)

Table 8d – Multivariable Analyses of Distance and Educational Achievement and having cancer on initial biopsy?

Variable	Categories	OR	95% CI	P-Value[#]
Education (relative to Illiterate)	Incomplete Primary	1.18	0.85 – 1.65	0.39
	Complete Primary	1.07	0.58 – 1.97	
	High School + College	0.79	0.29 – 2.13	
Distance (relative to 0 – 249.99 km)	250 – 499.99 km	1.06	0.76 – 1.47	0.34
	500 – 999.99 km	0.90	0.55 – 1.46	
	$\geq$ 1000 km	1.49	0.94 – 2.38	

Statistical Analyses: Logistic Regression, # = Likelihood Ratio Test
Multivariable Analysis adjusted for Age
CI = confidence interval; km = kilometers; PC = prostate cancer

Table 9 – The Association between Education and Distance and Biopsy Cancer Grade Relative to no cancer (n=858)

Table 9a – Is there an association between distance and cancer grade on initial biopsy?

Model	Categories	RRR	95% CI	P-Value[#]
Cancer Outcome: Low-Grade Cancer, Gleason < 7				
Distance (Relative to 0 – 249.99 km)				
Crude	**250 – 499.99 km**	**0.97**	**0.69 – 1.36**	**0.27**
	500 – 999.99 km	**0.86**	**0.53 – 1.41**	
	≥ 1000 km	**1.39**	**0.86 – 2.23**	
Adjusted for Age	250 – 499.99 km	0.97	0.69 – 1.37	0.26
	500 – 999.99 km	0.88	0.54 – 1.44	
	≥ 1000 km	1.42	0.88 – 2.29	
Adjusted for Total Number of Cores Taken	250 – 499.99 km	0.93	0.66 – 1.32	0.30
	500 – 999.99 km	0.83	0.51 – 1.36	
	≥ 1000 km	1.37	0.85 – 2.21	
Adjusted for Biopsy Year	250 – 499.99 km	0.93	0.66 – 1.32	0.32
	500 – 999.99 km	0.81	0.49 – 1.33	
	≥ 1000 km	1.34	0.83 – 2.17	
Adjusted for Family History of Any Cancer	250 – 499.99 km	0.92	0.65 – 1.30	0.29
	500 – 999.99 km	0.81	0.49 – 1.33	
	≥ 1000 km	1.38	0.85 – 2.23	
Adjusted for Family History of PC	250 – 499.99 km	0.92	0.65 – 1.30	0.29
	500 – 999.99 km	0.81	0.49 – 1.33	
	≥ 1000 km	1.38	0.85 – 2.23	
Cancer Outcome: High-Grade Cancer, Gleason ≥ 7				
Crude	250 – 499.99 km	2.44	1.03 – 5.79	0.27
	500 – 999.99 km	0.96	0.21 – 4.51	
	≥ 1000 km	2.41	0.73 – 7.99	
Adjusted for Age	**250 – 499.99 km**	**2.38**	**0.99 – 5.74**	**0.26**
	500 – 999.99 km	**1.10**	**0.23 – 5.26**	
	≥ 1000 km	**2.93**	**0.86 – 9.98**	
Adjusted for Total Number of Cores Taken	**250 – 499.99 km**	**2.23**	**0.92 – 5.40**	**0.30**
	500 – 999.99 km	**0.98**	**0.21 – 4.72**	
	≥ 1000 km	**2.69**	**0.79 – 9.20**	
Adjusted for Biopsy Year	250 – 499.99 km	2.23	0.92 – 5.41	0.32
	500 – 999.99 km	0.85	0.17 – 4.16	

	≥ 1000 km	2.35	0.68 – 8.16	
Adjusted for Family History of Any Cancer	250 – 499.99 km	2.20	0.92 – 5.34	0.29
	500 – 999.99 km	0.85	0.17 – 4.17	
	≥ 1000 km	2.44	0.70 – 8.55	
Adjusted for Family History of PC	250 – 499.99 km	2.19	0.90 – 5.34	0.29
	500 – 999.99 km	0.86	0.18 – 4.20	
	≥ 1000 km	2.44	0.70 – 8.54	

Statistical Analyses: Multinomial Logistic Regression; # = Likelihood Ratio Test
Educational Attainment defined as: Low-Education (Illiterate, Incomplete Primary) vs. High-Education (Complete Primary, High School, College)
CI = confidence interval; Km = kilometers; PC = prostate cancer; RRR = relative risk ratio

Table 9 – The Association between Education and Distance and Biopsy Cancer Grade Relative to no cancer (n=858) (continued)

Table 9b – Is there an association between educational achievement and cancer grade on initial biopsy?

Model	RRR	95% CI	P-Value
Cancer Outcome: Low-Grade Cancer, Gleason < 7			
Educational Attainment (Relative to Low-Education)			
Crude	0.75	0.45 – 1.23	0.25
Adjusted for Age	**0.83**	**0.50 – 1.37**	**0.46**
Adjusted for Total Number of Cores Taken	**0.83**	**0.50 – 1.39**	**0.48**
Adjusted for Biopsy Year	**0.86**	**0.52 – 1.43**	**0.57**
Adjusted for Family History of Any Cancer	0.85	0.51 – 1.42	0.54
Adjusted for Family History of PC	0.85	0.51 – 1.42	0.53
Cancer Outcome: High-Grade Cancer, Gleason ≥ 7			
Crude	1.01	0.30 – 3.45	0.99
Adjusted for Age	**1.38**	**0.39 – 4.88**	**0.62**
Adjusted for Total Number of Cores Taken	**1.45**	**0.41 – 5.15**	**0.57**
Adjusted for Biopsy Year	**1.69**	**0.47 – 6.11**	**0.43**
Adjusted for Family History of Any Cancer	1.68	0.46 – 6.09	0.43
Adjusted for Family History of PC	1.68	0.46 – 6.07	0.43

Statistical Analyses: Multinomial Logistic Regression
Educational Attainment defined as: Low-Education (Illiterate, Incomplete Primary) vs. High-Education (Complete Primary, High School, College)
CI = confidence interval; PC = prostate cancer; RRR = relative risk ratio

Table 9 – The Association between Education and Distance and Biopsy Cancer Grade Relative to no cancer (n=858) (continued)

Table 9c – Refined Multivariable Model of the Association between Distance and Education and cancer grade on initial biopsy.

Variable	Categories	RRR	95% CI	P-Value
Cancer Outcome: Low-Grade Cancer, Gleason < 7				
Education (relative to Low-Education)		0.87	0.50 – 1.51	0.61
Distance (relative to 0 – 249.99 km)	250 – 499.99 km	0.93	0.65 – 1.32	0.36#
	500 – 999.99 km	0.80	0.48 – 1.36	
	≥ 1000 km	1.34	0.69 – 2.62	
Age		1.03	1.01 – 1.04	0.002
Biopsy Year		1.16	0.98 – 1.38	0.08
Total Number of Cores Taken		1.03	0.97 – 1.09	0.34
Distance x Education				0.97
Cancer Outcome: High-Grade Cancer, Gleason ≥ 7				
Education (relative to Low-Education)		1.79	0.44 – 7.32	0.42
Distance (relative to 0 – 249.99 km)	250 – 499.99 km	2.25	0.92 – 5.50	0.36#
	500 – 999.99 km	0.89	0.18 – 4.51	
	≥ 1000 km	2.63	0.57 – 12.18	
Age		1.12	1.07 – 1.17	<0.001
Biopsy Year		1.71	1.08 – 2.69	0.02
Total Number of Cores Taken		1.03	0.88 – 1.20	0.71
Distance x Education				0.80

Statistical Analyses: Multinomial Logistic Regression, # = Likelihood Ratio Test
Educational Attainment defined as: Low-Education (Illiterate, Incomplete Primary) vs. High-Education (Complete Primary, High School, College)
Multivariable analysis adjusted for Age, Biopsy Year and Total Number of Cores Taken
CI = confidence interval; Km = kilometers; PC = prostate cancer; RRR = relative risk ratio

Table 9 – The Association between Education and Distance and Biopsy Cancer Grade Relative to no cancer (n=858) (continued)

Table 9d – Multivariable Analyses of Distance and Educational Achievement and cancer grade on initial biopsy?

Variable	Categories	RRR	95% CI	P-Value
Cancer Outcome: Low-Grade Cancer, Gleason < 7				
Education (relative to Low Education)		0.86	0.52 – 1.44	0.57
Distance (relative to 0 – 249.99 km)	250 – 499.99 km	0.93	0.66 – 1.32	0.32#
	500 – 999.99 km	0.80	0.49 – 1.32	
	≥ 1000 km	1.33	0.82 – 2.15	
Cancer Outcome: High-Grade Cancer, Gleason ≥ 7				
Education (relative to Low-Education)		1.65	0.46 – 6.00	0.44
Distance (relative to 0 – 249.99 km)	250 – 499.99 km	2.22	0.91 – 5.39	0.32#
	500 – 999.99 km	0.86	0.18 – 4.18	
	≥ 1000 km	2.34	0.67 – 8.13	

Statistical Analyses: Multinomial Logistic Regression, # = Likelihood Ratio Test
Educational Attainment defined as: Low-Education (Illiterate, Incomplete Primary) vs. High-Education (Complete Primary, High School, College)
Multivariable analysis adjusted for Age, Biopsy Year and Total Number of Cores Taken
CI = confidence interval; Km = kilometers; PC = prostate cancer; RRR = relative risk ratio

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